=> fil lreg

FILE 'LREGISTRY' ENTERED AT 14:53:13 ON 31 JAN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 1985 AMERICAN CHEMICAL SOCIETY (ACS)

LREGISTRY IS A STATIC LEARNING FILE

=> fil reg

FILE 'REGISTRY' ENTERED AT 14:53:15 ON 31 JAN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 30 JAN 2005 HIGHEST RN 823177-37-3
DICTIONARY FILE UPDATES: 30 JAN 2005 HIGHEST RN 823177-37-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> fil hcap

FILE 'HCAPLUS' ENTERED AT 14:53:18 ON 31 JAN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
the American Chemical Society and is provided to assist you in searching
databases on STN. Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.

FILE COVERS 1907 - 31 Jan 2005 VOL 142 ISS 6
FILE LAST UPDATED: 30 Jan 2005 (20050130/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> fil medlin

FILE 'MEDLINE' ENTERED AT 14:53:21 ON 31 JAN 2005

FILE LAST UPDATED: 29 JAN 2005 (20050129/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

Warning: The search L-number/HUMAN limit is missing from records indexed with the new 2005 MeSH (records added since December 19, 2004). Until this is corrected, include HUMANS/CT and 20041219-20051231/ED in searches to limit results to humans for this time period.

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil biosis

FILE 'BIOSIS' ENTERED AT 14:53:23 ON 31 JAN 2005
Copyright (c) 2005 The Thomson Corporation.

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 26 January 2005 (20050126/ED)

FILE RELOADED: 19 October 2003.

=> fil embase

FILE 'EMBASE' ENTERED AT 14:53:26 ON 31 JAN 2005
COPYRIGHT (C) 2005 Elsevier Inc. All rights reserved.

FILE COVERS 1974 TO 27 Jan 2005 (20050127/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil drugu

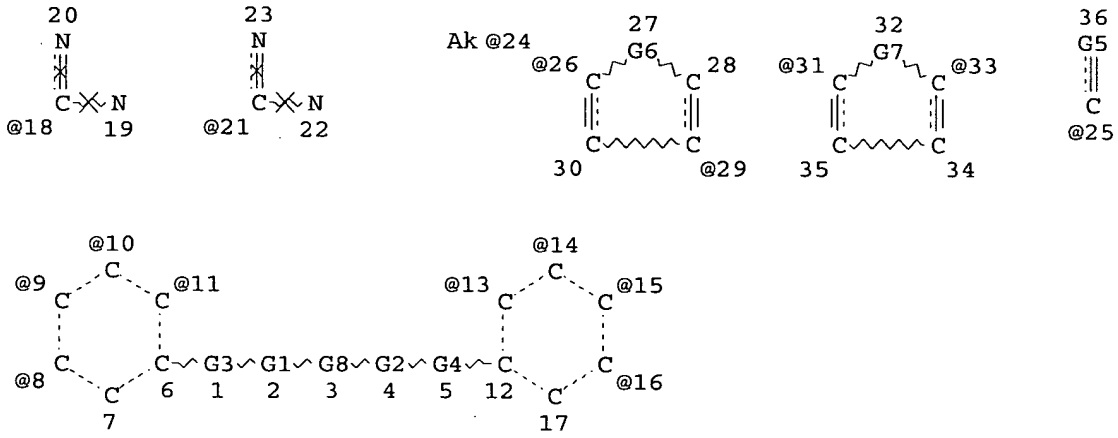
FILE 'DRUGU' ENTERED AT 14:53:29 ON 31 JAN 2005
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

FILE LAST UPDATED: 26 JAN 2005 <20050126/UP>
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<
>>> THESAURUS AVAILABLE IN /CT <<<

>>> A RECENT REVIEW OF PSYCHIATRIC DISEASE KEYWORDS USED IN DERWENT DRUG FILE HAS PROMPTED A REVISION BASED

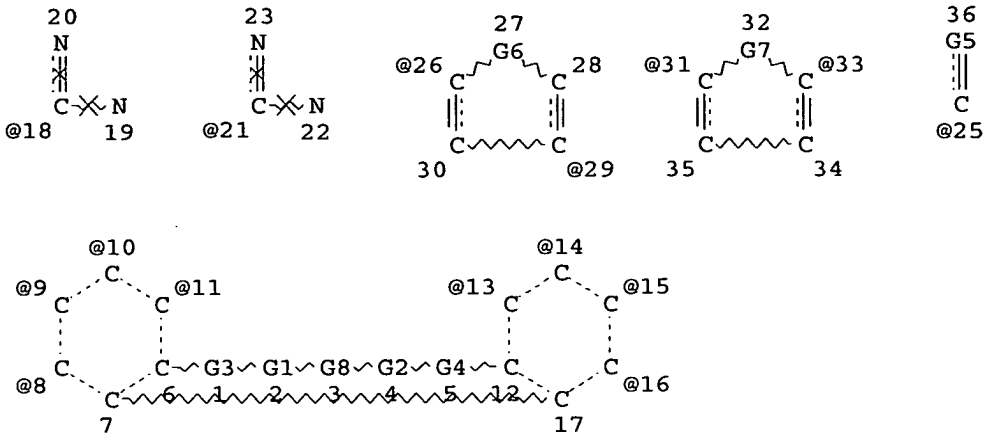
```
     ON STANDARD TERMS USED IN DSM-IV (DIAGNOSTIC AND
     STATISTICAL MANUAL OF MENTAL DISORDERS - FOURTH
     EDITION).
     FOR FURTHER DETAILS:
http://thomsonderwent.com/derwenthome/support/userguides/lit_guide


=> fil wpix

FILE 'WPIX' ENTERED AT 14:53:34 ON 31 JAN 2005
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

FILE LAST UPDATED:          28 JAN 2005      <20050128/UP>
MOST RECENT DERWENT UPDATE:     200507        <200507/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
    http://thomsonderwent.com/coverage/latestupdates/           <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://thomsonderwent.com/support/userguides/               <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT
    DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
    FIRST VIEW - FILE WPIFV.
    FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv  <<<

>>> NEW DISPLAY FORMAT HITSTR ADDED ALLOWING DISPLAY OF
    HIT STRUCTURES WITHIN THE BIBLIOGRAPHIC DOCUMENT  <<<

>>> SMILES and ISOSMILES strings are no longer available as
    Derwent Chemistry Resource display fields  <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.
    PLEASE CHECK:
http://thomsonderwent.com/support/dwpiref/reftools/classification/code-revision/
    FOR DETAILS. <<<

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 14:53:37 ON 31 JAN 2005
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jan 28, 2005 (20050128/UP).

=>
=> => d que l33
L1   (   2453254)SEA FILE=REGISTRY ABB=ON  PLU=ON  (N>=4 AND C6/ES AND CNRS>=3)
                  NOT (PMS/CI OR MNS/CI OR AYS/CI OR SEQUENCE/FS)
L2                SCR 1256 2100 1840
L3                STR
```



VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G5=O/S/N
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=24/25/26-2 29-4/29-2 26-4/31-2 33-4
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
CONNECT IS E2 RC AT 24
DEFAULT MLEVEL IS ATOM
GGCAT IS SAT AT 24
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS M2-X6 C AT 24

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 36

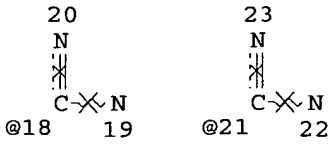
STEREO ATTRIBUTES: NONE
L4 (171) SEA FILE=REGISTRY SUB=L1 SSS FUL (L2 AND L3)
L5 SCR 1257
L6 (314) SEA FILE=REGISTRY SSS FUL (L5 AND L3)
L7 STR

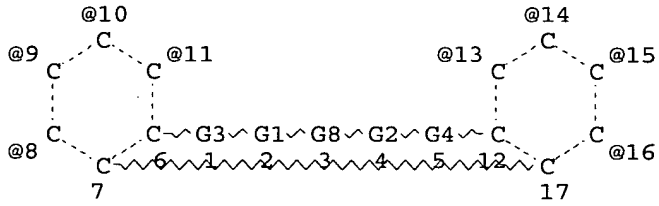


VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G5=O/S/N
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=25/26-2 29-4/29-2 26-4/31-2 33-4
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE
L8 STR

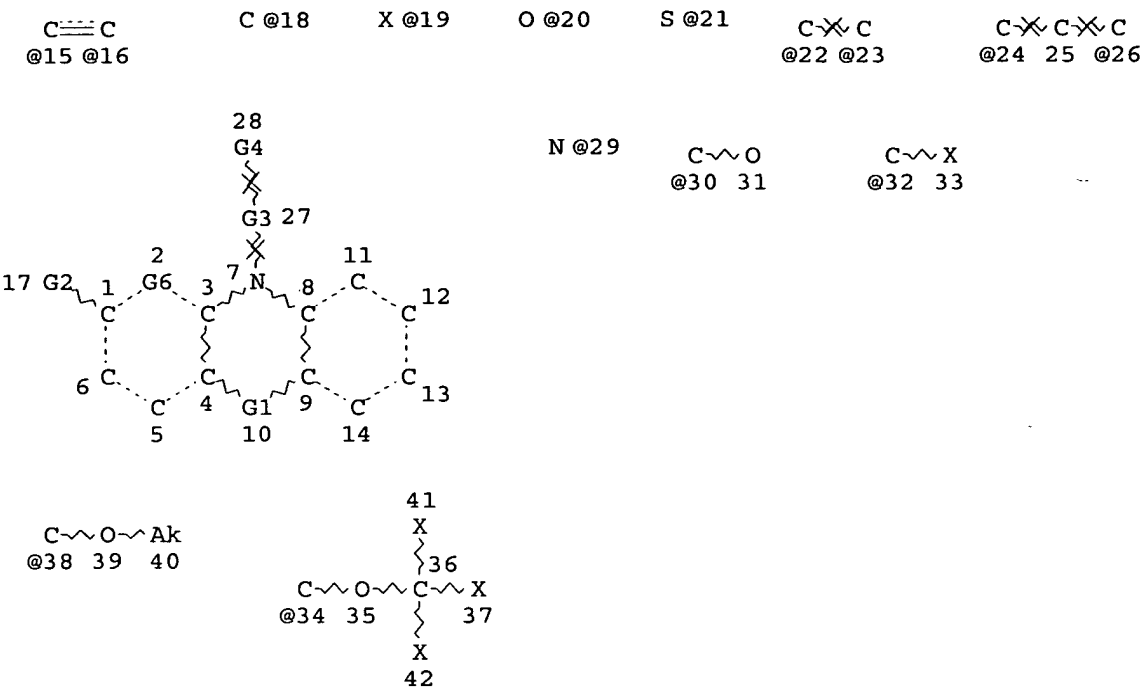




VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
REP G8=(2-6) CH2
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 23

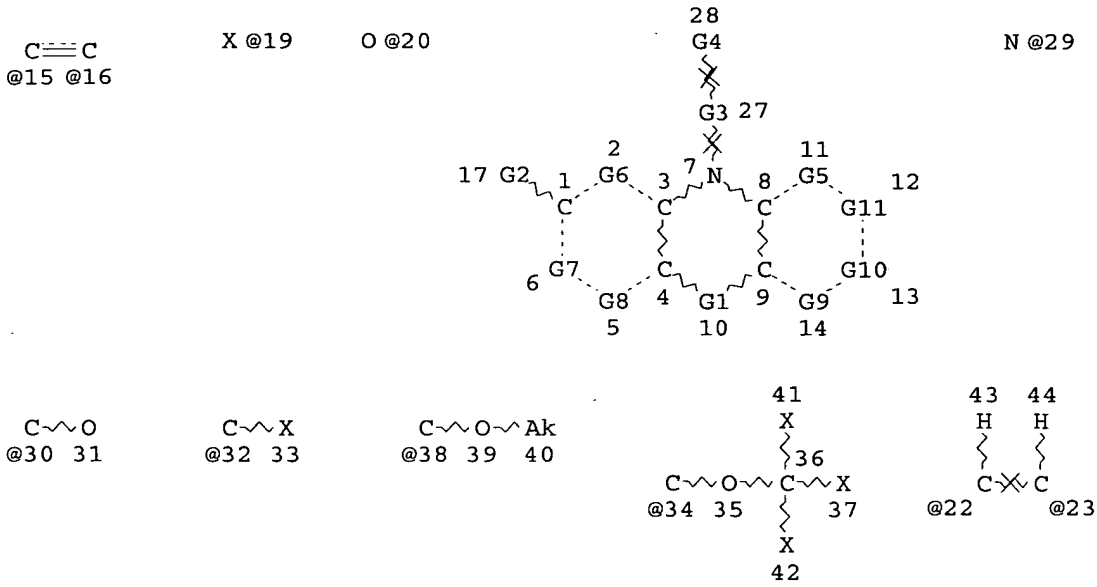
STEREO ATTRIBUTES: NONE
L9 (7) SEA FILE=REGISTRY SSS FUL L7
L10 (14) SEA FILE=REGISTRY SSS FUL L8
L11 (14) SEA FILE=REGISTRY ABB=ON PLU=ON L9 OR L10
L12 STR

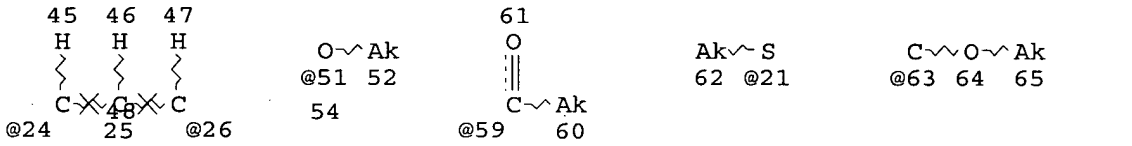


VAR G1=O/S/N/CH2/15-4 16-9
VAR G2=18/19/20/21
VAR G3=22-7 23-28/24-7 26-28
VAR G4=20/29
VAR G6=CH/30/32/34/38
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
NSPEC IS RC AT 24
NSPEC IS RC AT 25
NSPEC IS RC AT 26
NSPEC IS RC AT 29
CONNECT IS E1 RC AT 31
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

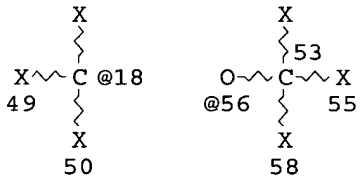
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 42

STEREO ATTRIBUTES: NONE
L13 (9125) SEA FILE=REGISTRY SSS FUL L12
L14 STR



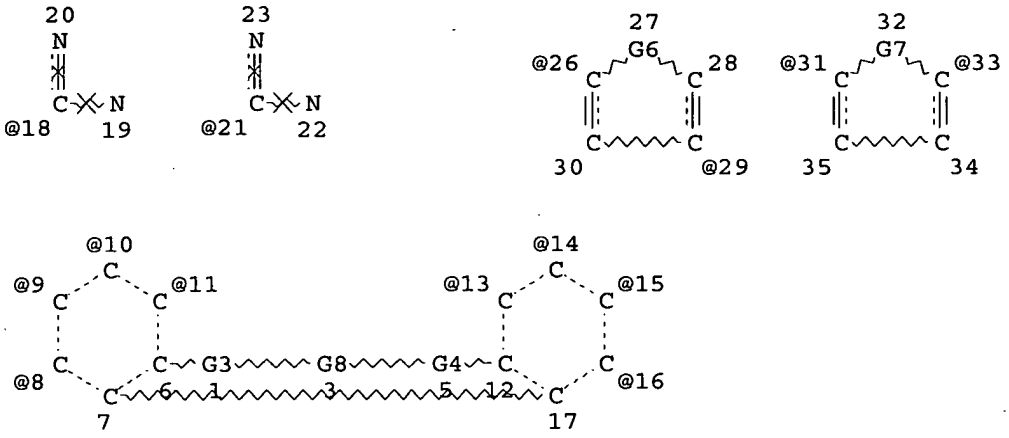


Page 1-A

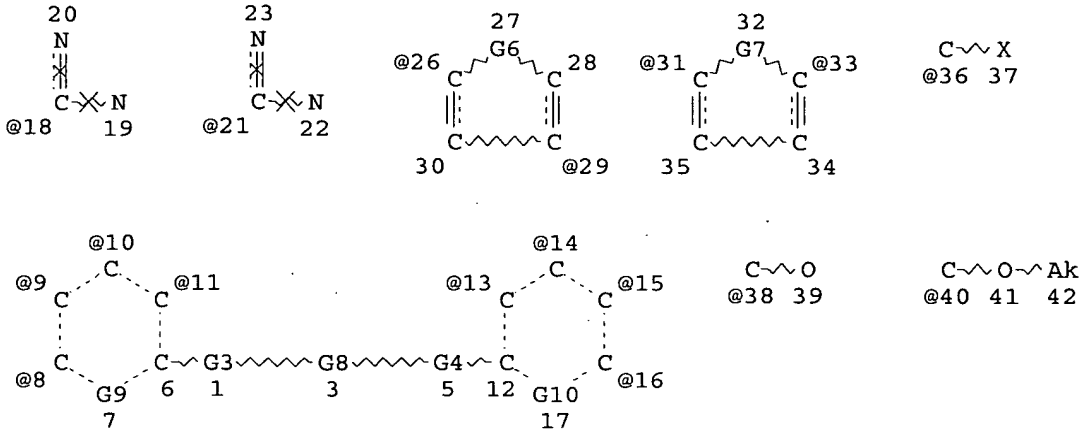


Page 2-A
VAR G1=O/S/NH/CH2/15-4 16-9
VAR G2=18/19/51/59/CN/56/21/63
VAR G3=22-7 23-28/24-7 26-28
VAR G4=20/29
VAR G5=CH/30/32/34/38
VAR G6=CH/30/32/34/38
VAR G7=CH/30/32/34/38
VAR G8=CH/30/32/34/38
VAR G9=CH/30/32/34/38
VAR G10=CH/30/32/34/38
VAR G11=CH/30/32/34/38
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
NSPEC IS RC AT 24
NSPEC IS RC AT 25

```
NSPEC   IS RC     AT  26
NSPEC   IS RC     AT  29
CONNECT IS E1  RC AT  31
CONNECT IS E1  RC AT  52
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  64

STEREO ATTRIBUTES: NONE
L15 (      5920)SEA FILE=REGISTRY SUB=L13 SSS FUL L14
L16             STR
```

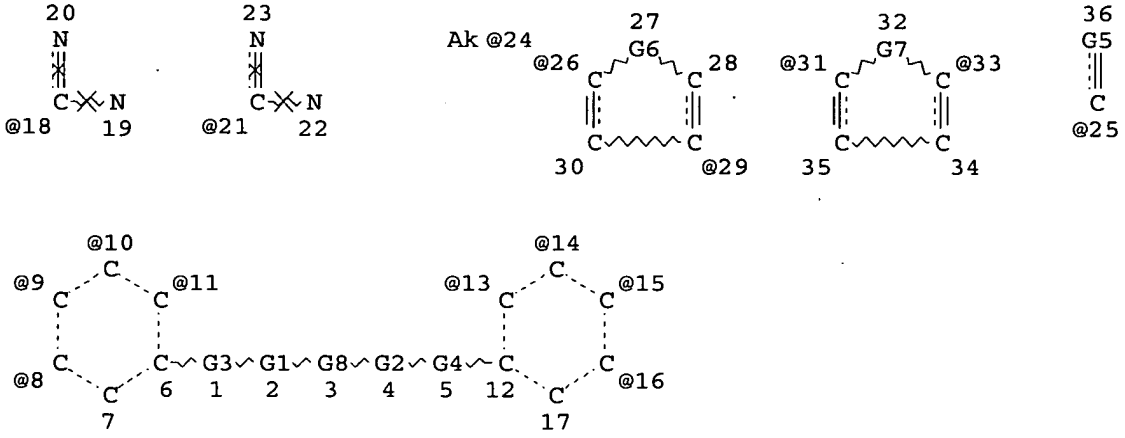



```
REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=26-1 29-5/29-1 26-5/31-1 33-5
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
NSPEC   IS RC     AT  20
NSPEC   IS RC     AT  21
NSPEC   IS RC     AT  22
NSPEC   IS RC     AT  23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  31

STEREO ATTRIBUTES: NONE
L17             STR
```



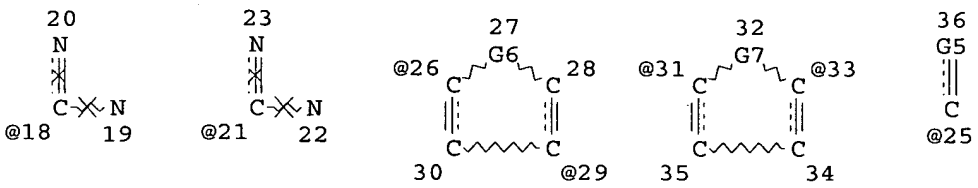
```
REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=26-1 29-5/29-1 26-5/31-1 33-5
VAR G9=CH/36/38/40/43/45
VAR G10=CH/36/38/40/43/45
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
NSPEC   IS RC     AT  20
NSPEC   IS RC     AT  21
NSPEC   IS RC     AT  22
NSPEC   IS RC     AT  23
CONNECT IS E1  RC AT  39
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC  12   6
NUMBER OF NODES IS  42

STEREO ATTRIBUTES: NONE
L18              SCR 1841
L19 (         86)SEA FILE=REGISTRY SUB=L1 SSS FUL (L18 AND L2 AND L17)
L20 (        240)SEA FILE=REGISTRY SSS FUL (L5 AND L17)
L21 (          7)SEA FILE=REGISTRY SSS FUL L16
L22 (        801)SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 OR L4 OR L11 OR L19 OR
                 L20 OR L21
L23 (          0)SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND L22
L24 (      22283)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15
L25 (       1470)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 OR L23
L26 (         36)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L24 AND L25
L27 (         34)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L26 AND (PHARM?)/SC,SX
L28 (      13427)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 (L) (BIOL+NT)/RL
```

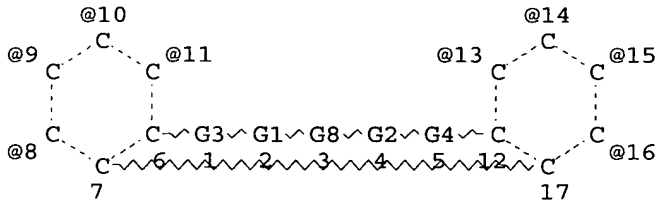
```
L29 (      1047)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L22 OR L23) (L) (BIOL+NT)/RL

L30 (        29)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L28 AND L29
L31 (        34)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L27 OR L30
L32 (    946303)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (?NEOPLAS? OR ?CANCER? OR
                ?CARCIN? OR ?SARCOMA? OR ?LYMPHOM? OR ?MELANOM? OR ?TUMOR? OR
                ?PROLIFERAT? OR ?LEUKEM? OR ?CHEMOTHERAP? OR ?MYOMA? OR
                ?HODGKIN?)
L33          11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L31 AND L32


=> d que l61
L34 (   2453254)SEA FILE=REGISTRY ABB=ON  PLU=ON  (N>=4 AND C6/ES AND CNRS>=3)
                NOT (PMS/CI OR MNS/CI OR AYS/CI OR SEQUENCE/FS)
L35             SCR 1256 2100 1840
L36             STR
```




```
VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G5=O/S/N
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=24/25/26-2 29-4/29-2 26-4/31-2 33-4
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
NSPEC   IS RC     AT  20
NSPEC   IS RC     AT  21
NSPEC   IS RC     AT  22
NSPEC   IS RC     AT  23
CONNECT IS E2  RC AT  24
DEFAULT MLEVEL IS ATOM
GGCAT   IS SAT  AT  24
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS M2-X6 C  AT  24

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  36
```

STEREO ATTRIBUTES: NONE
L37 (171)SEA FILE=REGISTRY SUB=L34 SSS FUL (L35 AND L36)
L38 SCR 1257
L39 (314)SEA FILE=REGISTRY SSS FUL (L38 AND L36)
L40 STR

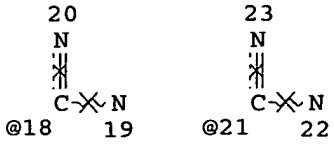


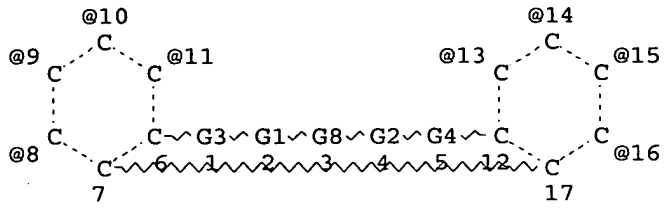


VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G5=O/S/N
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=25/26-2 29-4/29-2 26-4/31-2 33-4
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

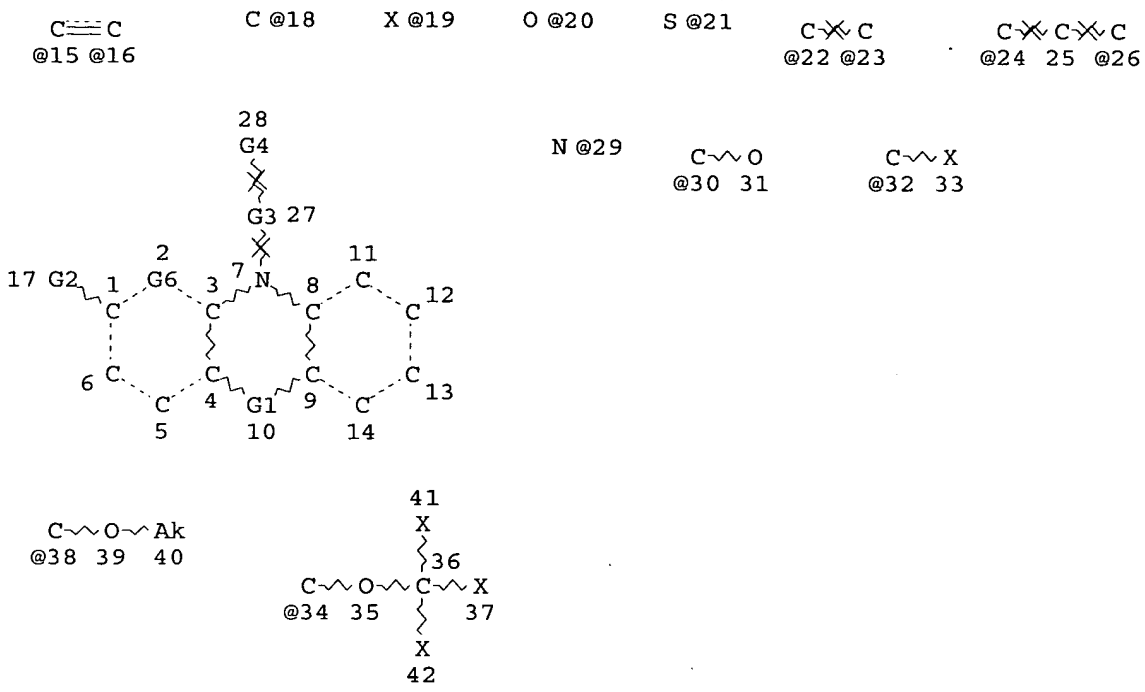
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE
L41 STR

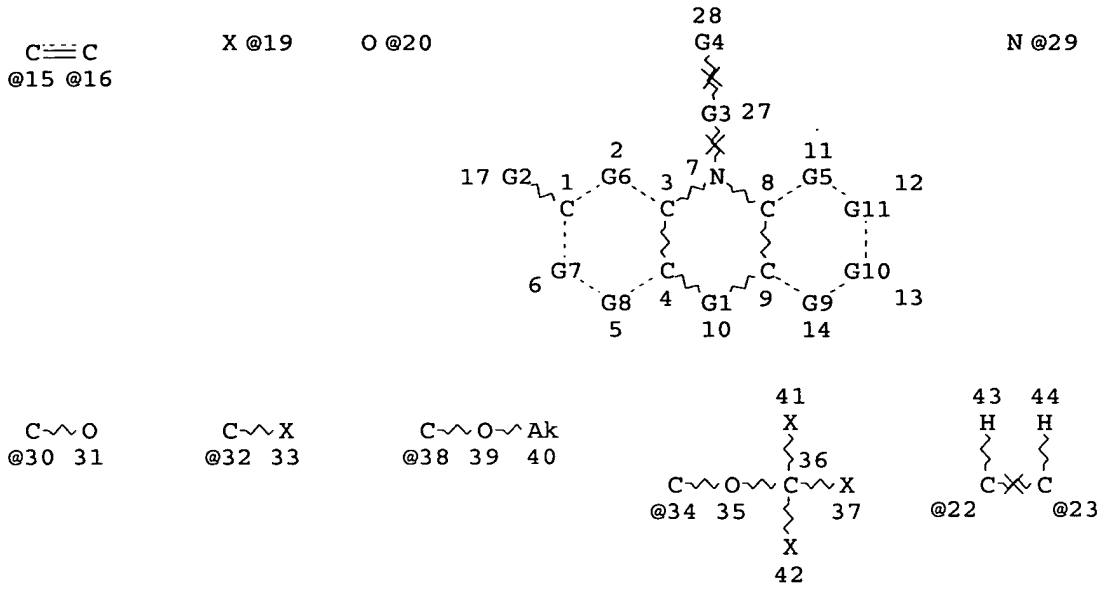




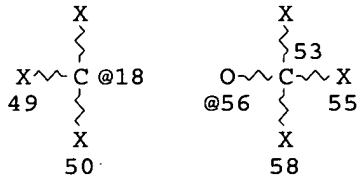

```
VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
REP G8=(2-6) CH2
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
NSPEC   IS RC     AT  20
NSPEC   IS RC     AT  21
NSPEC   IS RC     AT  22
NSPEC   IS RC     AT  23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  23

STEREO ATTRIBUTES: NONE
L42 (         7)SEA FILE=REGISTRY SSS FUL L40
L43 (        14)SEA FILE=REGISTRY SSS FUL L41
L44 (        14)SEA FILE=REGISTRY ABB=ON  PLU=ON  L42 OR L43
L45             STR
```




```
VAR G1=O/S/N/CH2/15-4 16-9
VAR G2=18/19/20/21
VAR G3=22-7 23-28/24-7 26-28
VAR G4=20/29
VAR G6=CH/30/32/34/38
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
NSPEC   IS RC     AT  20
NSPEC   IS RC     AT  21
NSPEC   IS RC     AT  22
NSPEC   IS RC     AT  23
NSPEC   IS RC     AT  24
NSPEC   IS RC     AT  25
NSPEC   IS RC     AT  26
NSPEC   IS RC     AT  29
CONNECT IS E1  RC AT  31
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  42

STEREO ATTRIBUTES: NONE
L46 (      9125) SEA FILE=REGISTRY SSS FUL L45
L47              STR
```



Page 1-A

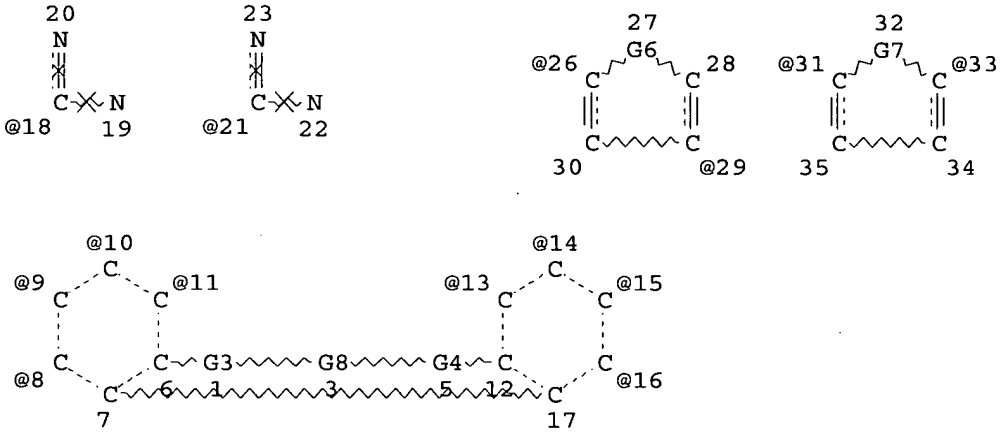


Page 2-A
VAR G1=O/S/NH/CH2/15-4 16-9
VAR G2=18/19/51/59/CN/56/21/63
VAR G3=22-7 23-28/24-7 26-28
VAR G4=20/29
VAR G5=CH/30/32/34/38
VAR G6=CH/30/32/34/38
VAR G7=CH/30/32/34/38
VAR G8=CH/30/32/34/38
VAR G9=CH/30/32/34/38
VAR G10=CH/30/32/34/38
VAR G11=CH/30/32/34/38
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
NSPEC IS RC AT 24
NSPEC IS RC AT 25

NSPEC IS RC AT 26
NSPEC IS RC AT 29
CONNECT IS E1 RC AT 31
CONNECT IS E1 RC AT 52
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 64

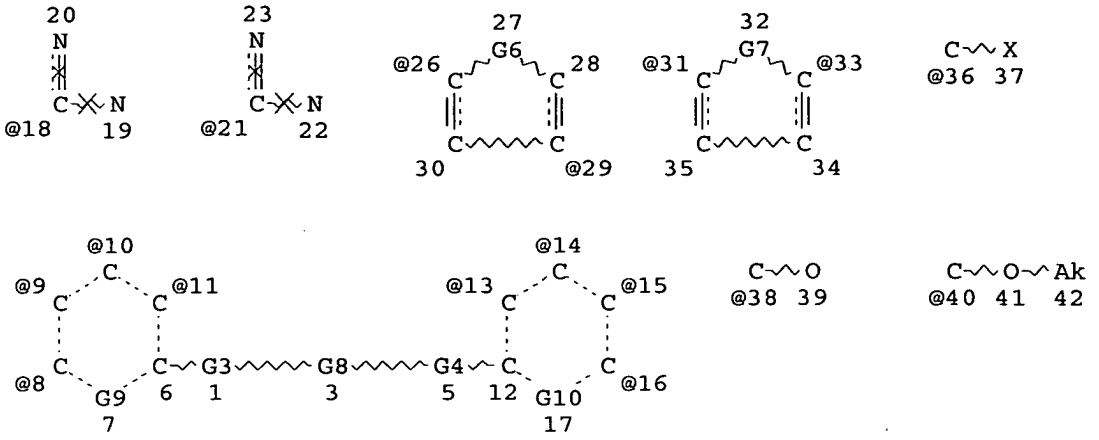
STEREO ATTRIBUTES: NONE
L48 (5920) SEA FILE=REGISTRY SUB=L46 SSS FUL L47
L49 STR



REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=26-1 29-5/29-1 26-5/31-1 33-5
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 31

STEREO ATTRIBUTES: NONE
L50 STR

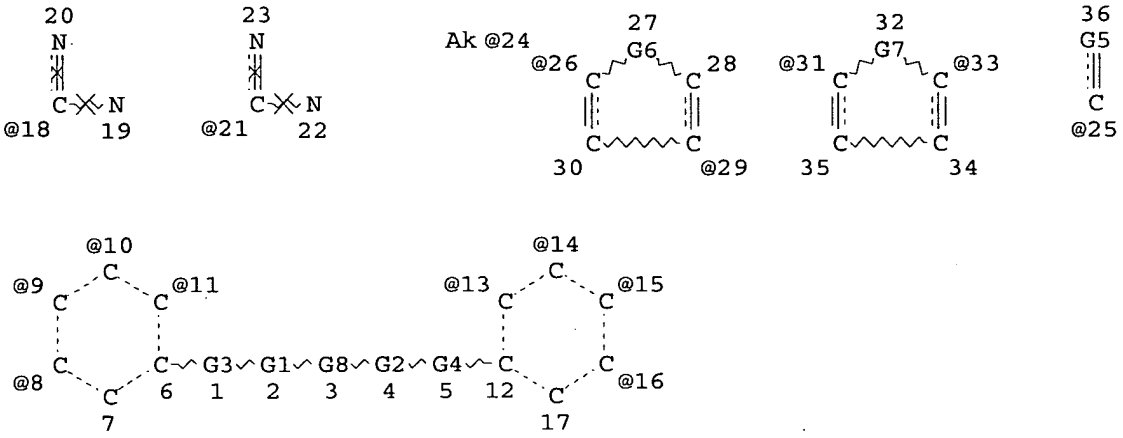


REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=26-1 29-5/29-1 26-5/31-1 33-5
VAR G9=CH/36/38/40/43/45
VAR G10=CH/36/38/40/43/45
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
CONNECT IS E1 RC AT 39
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

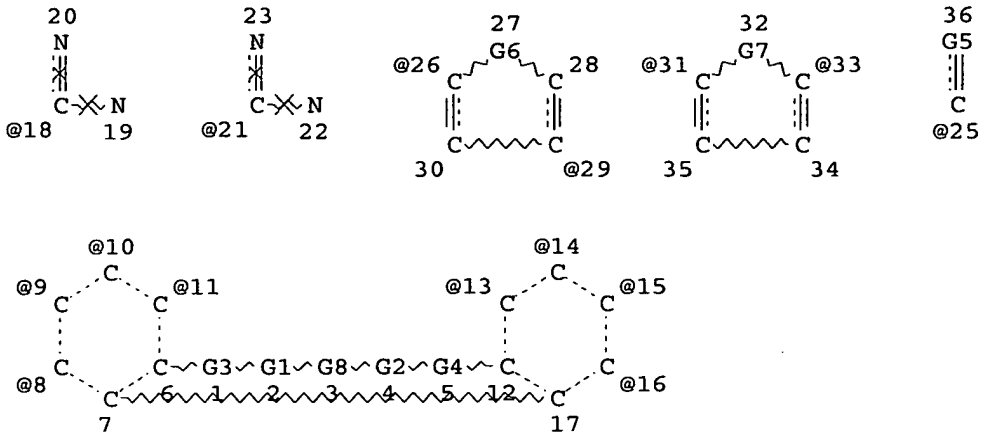
GRAPH ATTRIBUTES:
RSPEC 12 6
NUMBER OF NODES IS 42

STEREO ATTRIBUTES: NONE
L51 SCR 1841
L52 (86) SEA FILE=REGISTRY SUB=L34 SSS FUL (L51 AND L35 AND L50)
L53 (240) SEA FILE=REGISTRY SSS FUL (L38 AND L50)
L54 (7) SEA FILE=REGISTRY SSS FUL L49
L55 (801) SEA FILE=REGISTRY ABB=ON PLU=ON L39 OR L37 OR L44 OR L52 OR L53 OR L54
L56 (0) SEA FILE=REGISTRY ABB=ON PLU=ON L48 AND L55
L57 (0) SEA FILE=MEDLINE ABB=ON PLU=ON L56
L58 (1737) SEA FILE=MEDLINE ABB=ON PLU=ON L55
L59 (24505) SEA FILE=MEDLINE ABB=ON PLU=ON L48
L60 (2) SEA FILE=MEDLINE ABB=ON PLU=ON L58 AND L59
L61 2 SEA FILE=MEDLINE ABB=ON PLU=ON L60 OR L57

```
=> d que l94
L62 (   2453254)SEA FILE=REGISTRY ABB=ON  PLU=ON  (N>=4 AND C6/ES AND CNRS>=3)
                NOT (PMS/CI OR MNS/CI OR AYS/CI OR SEQUENCE/FS)
L63             SCR 1256 2100 1840
L64             STR
```



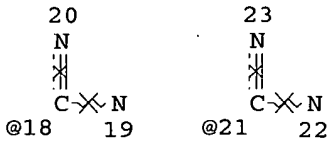

```
VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G5=O/S/N
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=24/25/26-2 29-4/29-2 26-4/31-2 33-4
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
NSPEC   IS RC     AT  20
NSPEC   IS RC     AT  21
NSPEC   IS RC     AT  22
NSPEC   IS RC     AT  23
CONNECT IS E2  RC AT  24
DEFAULT MLEVEL IS ATOM
GGCAT   IS SAT  AT  24
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS M2-X6 C  AT  24

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  36

STEREO ATTRIBUTES: NONE
L65 (       171)SEA FILE=REGISTRY SUB=L62 SSS FUL (L63 AND L64)
L66             SCR 1257
L67 (       314)SEA FILE=REGISTRY SSS FUL (L66 AND L64)
L68             STR
```

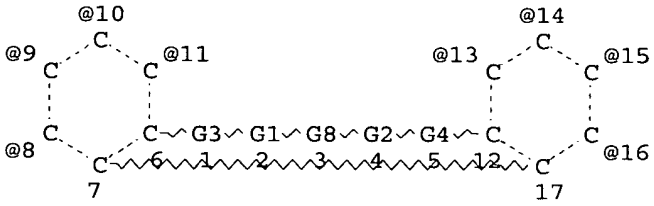


VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G5=O/S/N
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=25/26-2 29-4/29-2 26-4/31-2 33-4
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

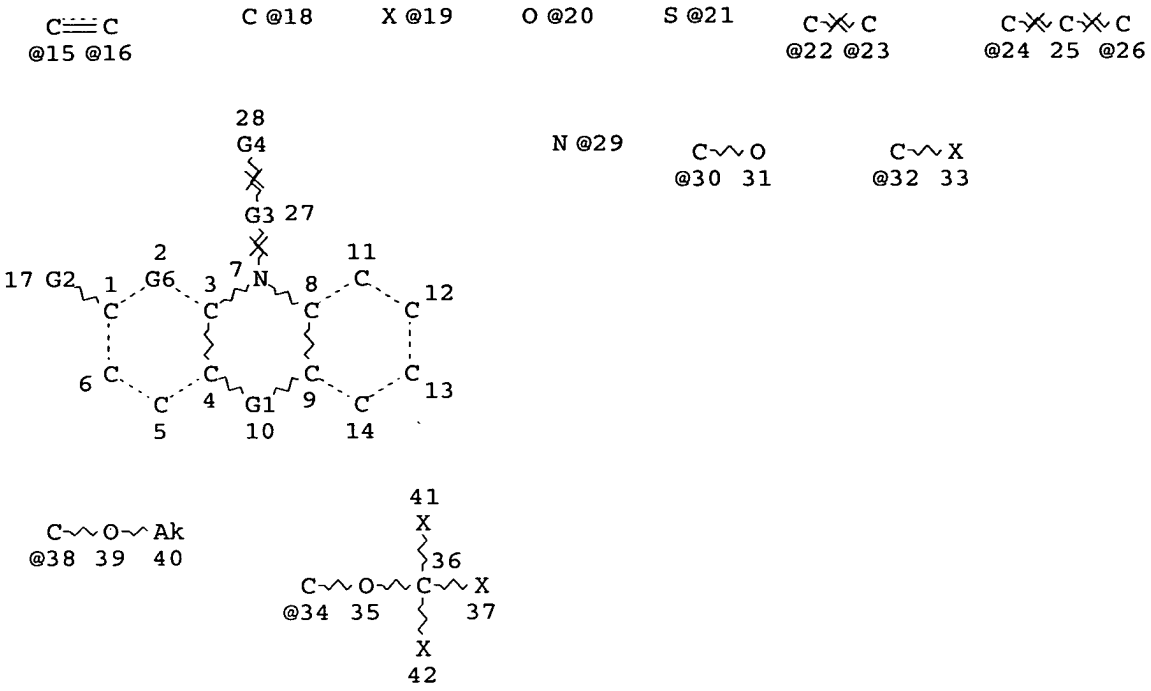
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE
L69 STR





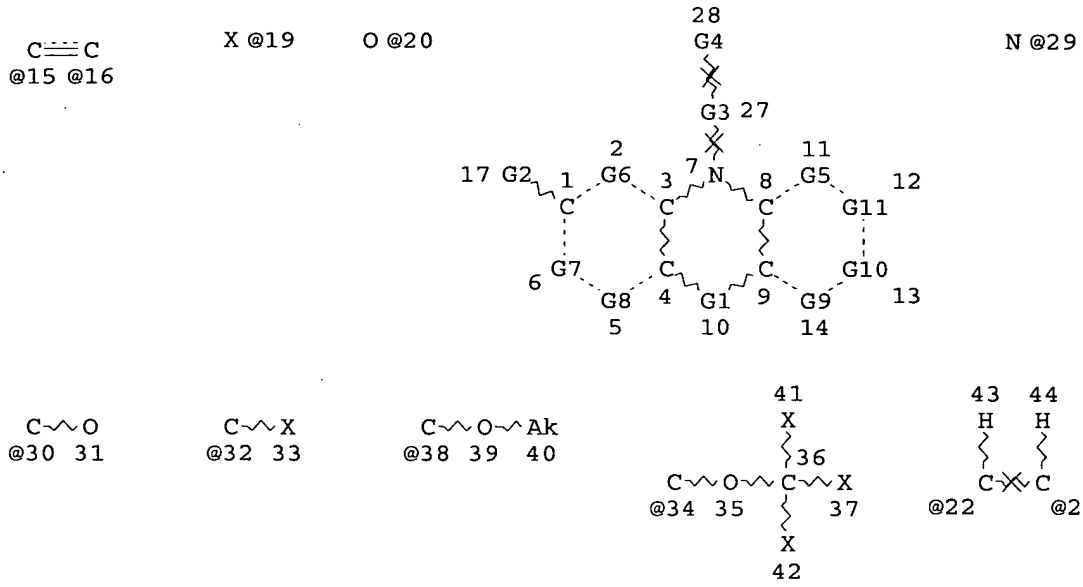

```
VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
REP G8=(2-6) CH2
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
NSPEC   IS RC     AT  20
NSPEC   IS RC     AT  21
NSPEC   IS RC     AT  22
NSPEC   IS RC     AT  23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  23

STEREO ATTRIBUTES: NONE
L70 (         7)SEA FILE=REGISTRY SSS FUL L68
L71 (        14)SEA FILE=REGISTRY SSS FUL L69
L72 (        14)SEA FILE=REGISTRY ABB=ON  PLU=ON  L70 OR L71
L73             STR
```



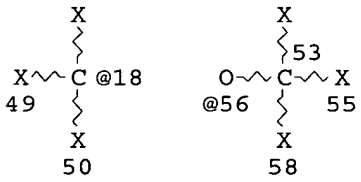
VAR G1=O/S/N/CH2/15-4 16-9
VAR G2=18/19/20/21
VAR G3=22-7 23-28/24-7 26-28
VAR G4=20/29
VAR G6=CH/30/32/34/38
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
NSPEC IS RC AT 24
NSPEC IS RC AT 25
NSPEC IS RC AT 26
NSPEC IS RC AT 29
CONNECT IS E1 RC AT 31
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 42

STEREO ATTRIBUTES: NONE
L74 (9125) SEA FILE=REGISTRY SSS FUL L73
L75 STR



Page 1-A

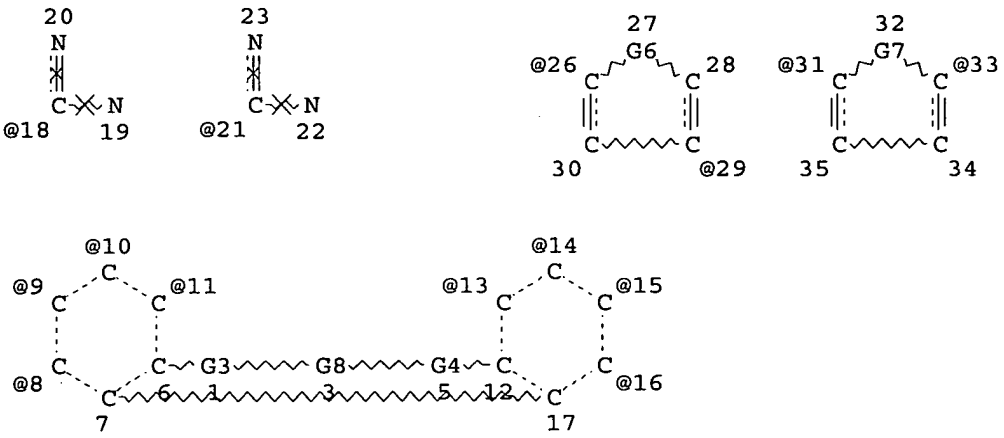


Page 2-A
VAR G1=O/S/NH/CH2/15-4 16-9
VAR G2=18/19/51/59/CN/56/21/63
VAR G3=22-7 23-28/24-7 26-28
VAR G4=20/29
VAR G5=CH/30/32/34/38
VAR G6=CH/30/32/34/38
VAR G7=CH/30/32/34/38
VAR G8=CH/30/32/34/38
VAR G9=CH/30/32/34/38
VAR G10=CH/30/32/34/38
VAR G11=CH/30/32/34/38
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
NSPEC IS RC AT 24
NSPEC IS RC AT 25

NSPEC IS RC AT 26
NSPEC IS RC AT 29
CONNECT IS E1 RC AT 31
CONNECT IS E1 RC AT 52
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 64

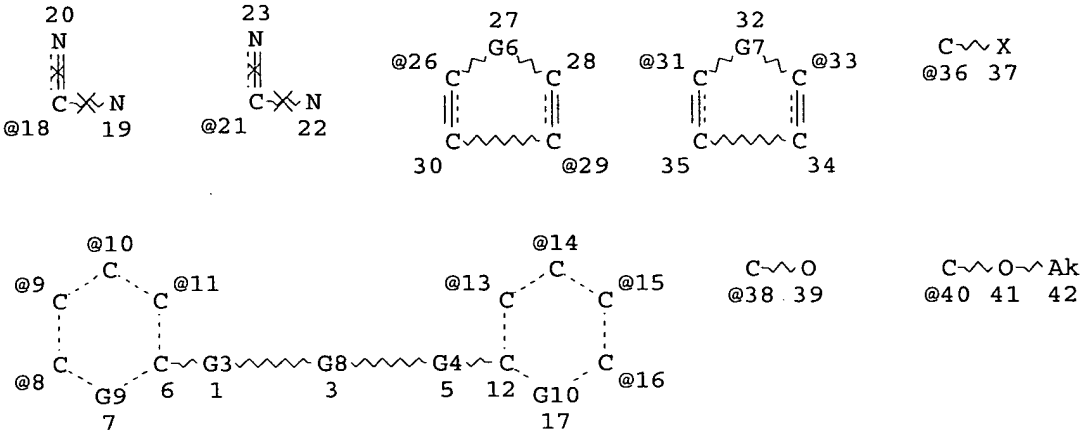
STEREO ATTRIBUTES: NONE
L76 (5920) SEA FILE=REGISTRY SUB=L74 SSS FUL L75
L77 STR



REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=26-1 29-5/29-1 26-5/31-1 33-5
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 31

STEREO ATTRIBUTES: NONE
L78 STR

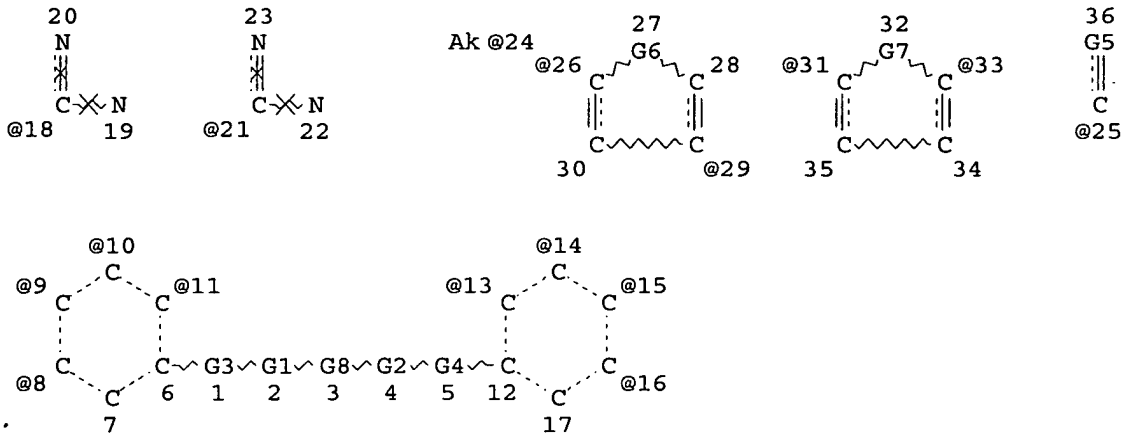


REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=26-1 29-5/29-1 26-5/31-1 33-5
VAR G9=CH/36/38/40/43/45
VAR G10=CH/36/38/40/43/45
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
CONNECT IS E1 RC AT 39
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 12 6
NUMBER OF NODES IS 42

STEREO ATTRIBUTES: NONE
L79 SCR 1841
L80 (86) SEA FILE=REGISTRY SUB=L62 SSS FUL (L79 AND L63 AND L78)
L81 (240) SEA FILE=REGISTRY SSS FUL (L66 AND L78)
L82 (7) SEA FILE=REGISTRY SSS FUL L77
L83 (801) SEA FILE=REGISTRY ABB=ON PLU=ON L67 OR L65 OR L72 OR L80 OR L81 OR L82
L84 (0) SEA FILE=REGISTRY ABB=ON PLU=ON L76 AND L83
L85 (19685) SEA FILE=BIOSIS ABB=ON PLU=ON L76
L86 (2105) SEA FILE=BIOSIS ABB=ON PLU=ON L83
L87 (0) SEA FILE=BIOSIS ABB=ON PLU=ON L84
L88 (9) SEA FILE=BIOSIS ABB=ON PLU=ON L85 AND L86
L89 (1807819) SEA FILE=BIOSIS ABB=ON PLU=ON (?NEOPLAS? OR ?CANCER? OR

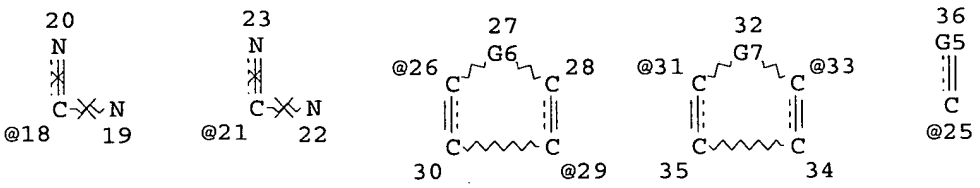
```
                ?CARCIN? OR ?SARCOMA? OR ?LYMPHOM? OR ?MELANOM? OR ?TUMOR? OR
                ?PROLIFERAT? OR ?LEUKEM? OR ?CHEMOTHERAP? OR ?MYOMA? OR
                ?HODGKIN?)
L90 (          2)SEA FILE=BIOSIS ABB=ON  PLU=ON  L88 AND L89
L91 (          2)SEA FILE=BIOSIS ABB=ON  PLU=ON  L87 OR L90
L92 (      30722)SEA FILE=BIOSIS ABB=ON  PLU=ON  ?ANGIOGEN?
L93 (          0)SEA FILE=BIOSIS ABB=ON  PLU=ON  L92 AND L88
L94            2 SEA FILE=BIOSIS ABB=ON  PLU=ON  L91 OR L93


=>

=> d que l130
L95 (    2453254)SEA FILE=REGISTRY ABB=ON  PLU=ON  (N>=4 AND C6/ES AND CNRS>=3)
                 NOT (PMS/CI OR MNS/CI OR AYS/CI OR SEQUENCE/FS)
L96              SCR 1256 2100 1840
L97              STR
```

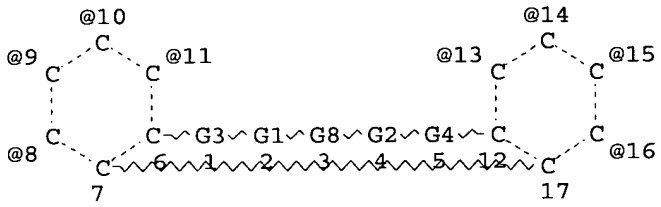



```
VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G5=O/S/N
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=24/25/26-2 29-4/29-2 26-4/31-2 33-4
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
NSPEC   IS RC     AT  20
NSPEC   IS RC     AT  21
NSPEC   IS RC     AT  22
NSPEC   IS RC     AT  23
CONNECT IS E2  RC AT  24
DEFAULT MLEVEL IS ATOM
GGCAT   IS SAT  AT  24
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS M2-X6 C  AT  24

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
```

NUMBER OF NODES IS 36

STEREO ATTRIBUTES: NONE
L98 (171) SEA FILE=REGISTRY SUB=L95 SSS FUL (L96 AND L97)
L99 SCR 1257
L100(314) SEA FILE=REGISTRY SSS FUL (L99 AND L97)
L101 STR

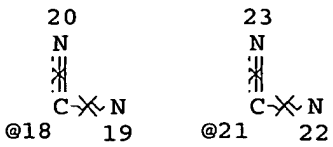


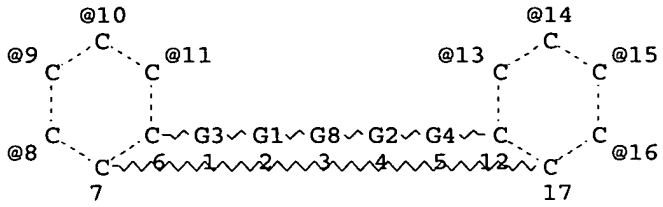


VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G5=O/S/N
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=25/26-2 29-4/29-2 26-4/31-2 33-4
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE
L102 STR

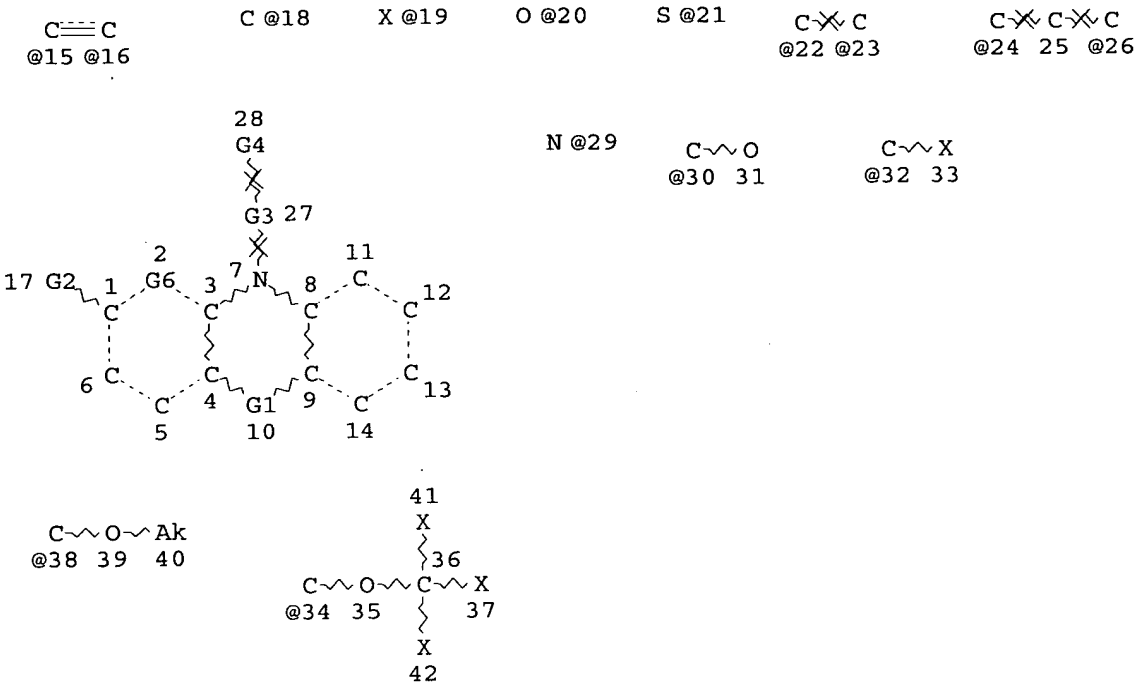




VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
REP G8=(2-6) CH2
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 23

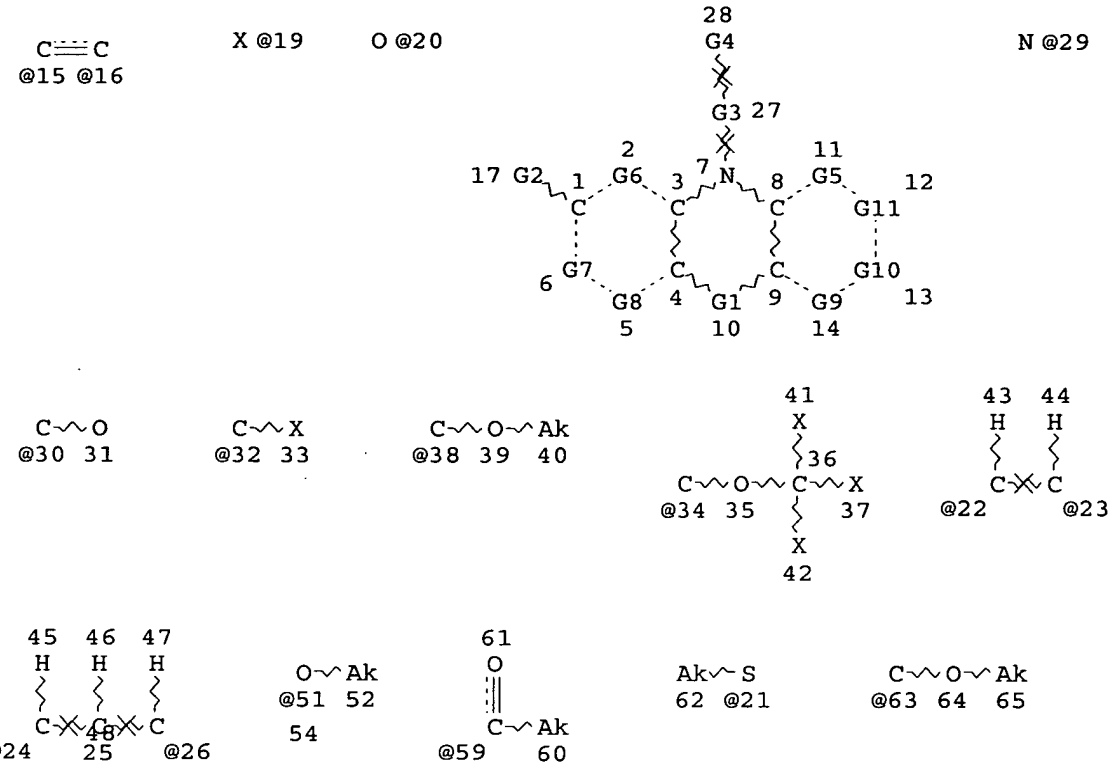
STEREO ATTRIBUTES: NONE
L103(7)SEA FILE=REGISTRY SSS FUL L101
L104(14)SEA FILE=REGISTRY SSS FUL L102
L105(14)SEA FILE=REGISTRY ABB=ON PLU=ON L103 OR L104
L106 STR



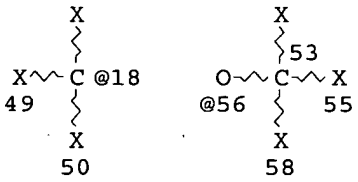
VAR G1=O/S/N/CH2/15-4 16-9
VAR G2=18/19/20/21
VAR G3=22-7 23-28/24-7 26-28
VAR G4=20/29
VAR G6=CH/30/32/34/38
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
NSPEC IS RC AT 24
NSPEC IS RC AT 25
NSPEC IS RC AT 26
NSPEC IS RC AT 29
CONNECT IS E1 RC AT 31
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 42

STEREO ATTRIBUTES: NONE
L107(9125)SEA FILE=REGISTRY SSS FUL L106
L108 STR



Page 1-A

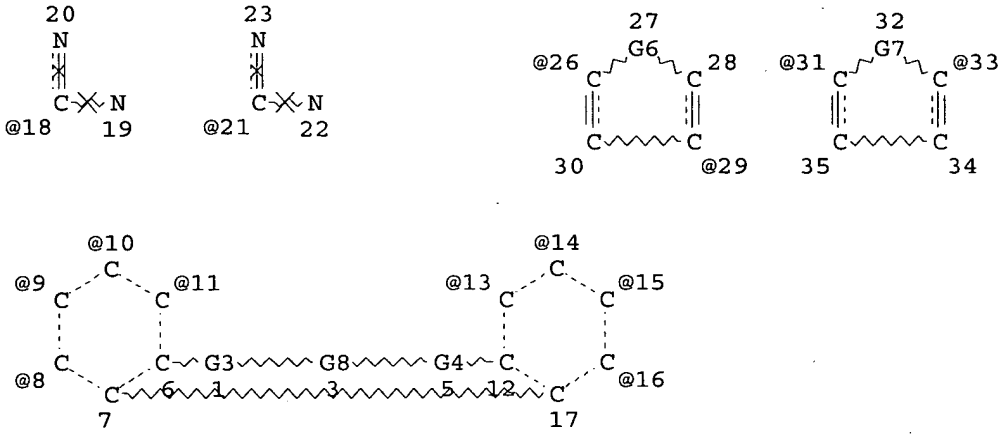


Page 2-A
VAR G1=O/S/NH/CH2/15-4 16-9
VAR G2=18/19/51/59/CN/56/21/63
VAR G3=22-7 23-28/24-7 26-28
VAR G4=20/29
VAR G5=CH/30/32/34/38
VAR G6=CH/30/32/34/38
VAR G7=CH/30/32/34/38
VAR G8=CH/30/32/34/38
VAR G9=CH/30/32/34/38
VAR G10=CH/30/32/34/38
VAR G11=CH/30/32/34/38
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
NSPEC IS RC AT 24
NSPEC IS RC AT 25

NSPEC IS RC AT 26
NSPEC IS RC AT 29
CONNECT IS E1 RC AT 31
CONNECT IS E1 RC AT 52
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 64

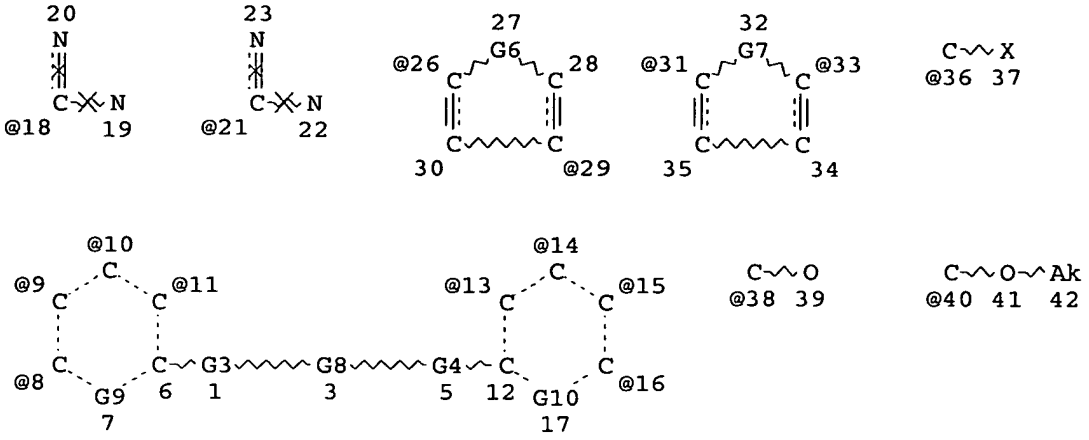
STEREO ATTRIBUTES: NONE
L109(5920)SEA FILE=REGISTRY SUB=L107 SSS FUL L108
L110 STR



REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=26-1 29-5/29-1 26-5/31-1 33-5
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 31

STEREO ATTRIBUTES: NONE
L111 STR

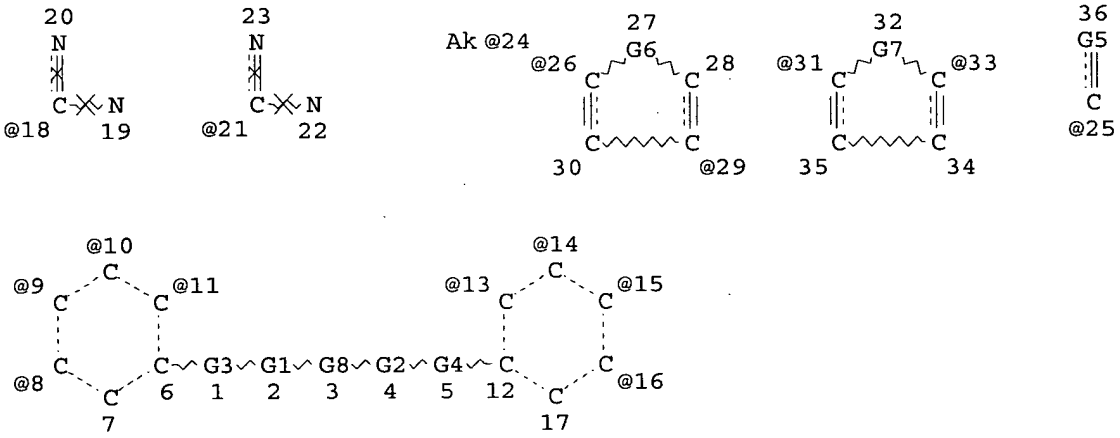


REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=26-1 29-5/29-1 26-5/31-1 33-5
VAR G9=CH/36/38/40/43/45
VAR G10=CH/36/38/40/43/45
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
CONNECT IS E1 RC AT 39
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 12 6
NUMBER OF NODES IS 42

STEREO ATTRIBUTES: NONE
L112 SCR 1841
L113(86)SEA FILE=REGISTRY SUB=L95 SSS FUL (L112 AND L96 AND L111)
L114(240)SEA FILE=REGISTRY SSS FUL (L99 AND L111)
L115(7)SEA FILE=REGISTRY SSS FUL L110
L116(801)SEA FILE=REGISTRY ABB=ON PLU=ON L100 OR L98 OR L105 OR L113
OR L114 OR L115
L117(0)SEA FILE=REGISTRY ABB=ON PLU=ON L109 AND L116
L118(0)SEA FILE=EMBASE ABB=ON PLU=ON L117
L119(5939)SEA FILE=EMBASE ABB=ON PLU=ON L116
L120(44068)SEA FILE=EMBASE ABB=ON PLU=ON L109
L121(133)SEA FILE=EMBASE ABB=ON PLU=ON L119 AND L120
L122(1610213)SEA FILE=EMBASE ABB=ON PLU=ON (?NEOPLAS? OR ?CANCER? OR

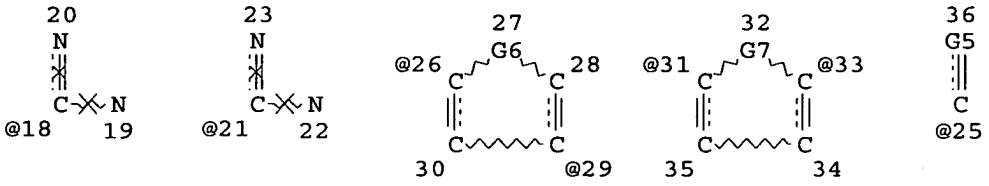
```
                ?CARCIN? OR ?SARCOMA? OR ?LYMPHOM? OR ?MELANOM? OR ?TUMOR? OR
                ?PROLIFERAT? OR ?LEUKEM? OR ?CHEMOTHERAP? OR ?MYOMA? OR
                ?HODGKIN?)
L123(         20)SEA FILE=EMBASE ABB=ON  PLU=ON  L121 AND L122
L124(     301328)SEA FILE=EMBASE ABB=ON  PLU=ON  DRUG COMBINATION+PFT,NT/CT
L125(     172544)SEA FILE=EMBASE ABB=ON  PLU=ON  DRUG INTERACTION+PFT,NT/CT
L126(      35213)SEA FILE=EMBASE ABB=ON  PLU=ON  COMBINATION CHEMOTHERAPY+PFT,NT
                /CT
L127(      31943)SEA FILE=EMBASE ABB=ON  PLU=ON  DRUG POTENTIATION+PFT,NT/CT
L128(         42)SEA FILE=EMBASE ABB=ON  PLU=ON  L121 AND (L124 OR L125 OR L126
                OR L127)
L129(          8)SEA FILE=EMBASE ABB=ON  PLU=ON  L123 AND L128
L130           8 SEA FILE=EMBASE ABB=ON  PLU=ON  L129 OR L118


=> d que l155
L131(   2453254)SEA FILE=REGISTRY ABB=ON  PLU=ON  (N>=4 AND C6/ES AND CNRS>=3)
                NOT (PMS/CI OR MNS/CI OR AYS/CI OR SEQUENCE/FS)
L132            SCR 1256 2100 1840
L133            STR
```

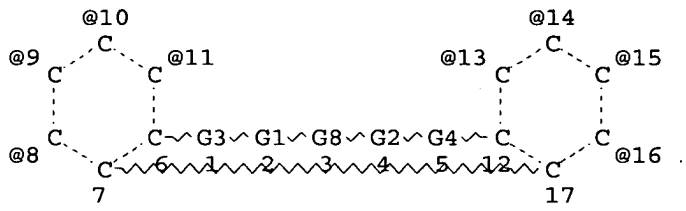



```
VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G5=O/S/N
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=24/25/26-2 29-4/29-2 26-4/31-2 33-4
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
NSPEC   IS RC     AT  20
NSPEC   IS RC     AT  21
NSPEC   IS RC     AT  22
NSPEC   IS RC     AT  23
CONNECT IS E2  RC AT  24
DEFAULT MLEVEL IS ATOM
GGCAT   IS SAT  AT  24
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS M2-X6 C  AT  24
```

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 36

STEREO ATTRIBUTES: NONE
L134 (171) SEA FILE=REGISTRY SUB=L131 SSS FUL (L132 AND L133)
L135 SCR 1257
L136 (314) SEA FILE=REGISTRY SSS FUL (L135 AND L133)
L137 STR

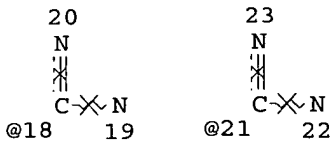


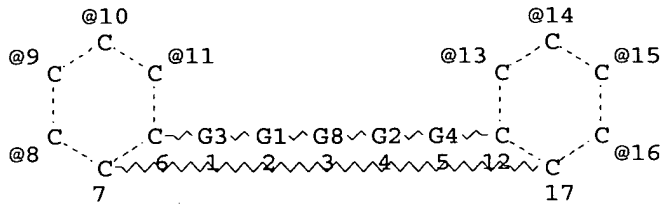


VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G5=O/S/N
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=25/26-2 29-4/29-2 26-4/31-2 33-4
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE
L138 STR

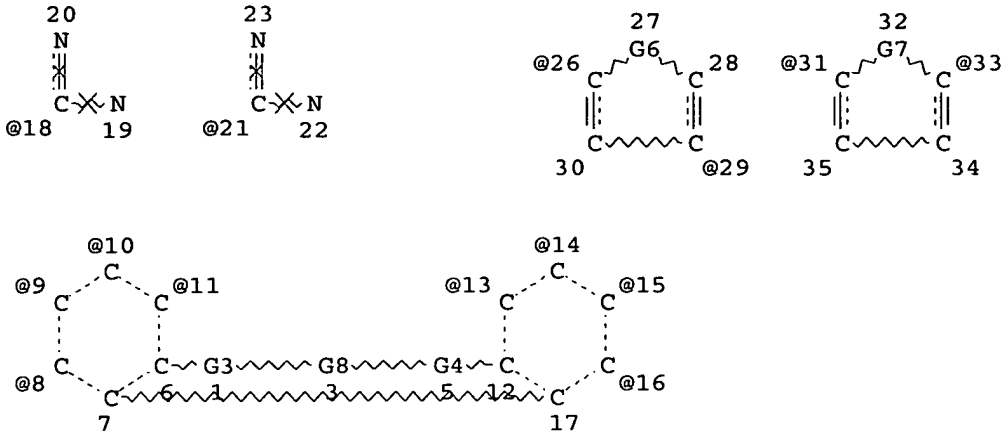




VAR G1=O/S/N
VAR G2=O/S/N
REP G3=(0-2) CH2
REP G4=(0-2) CH2
REP G8=(2-6) CH2
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 23

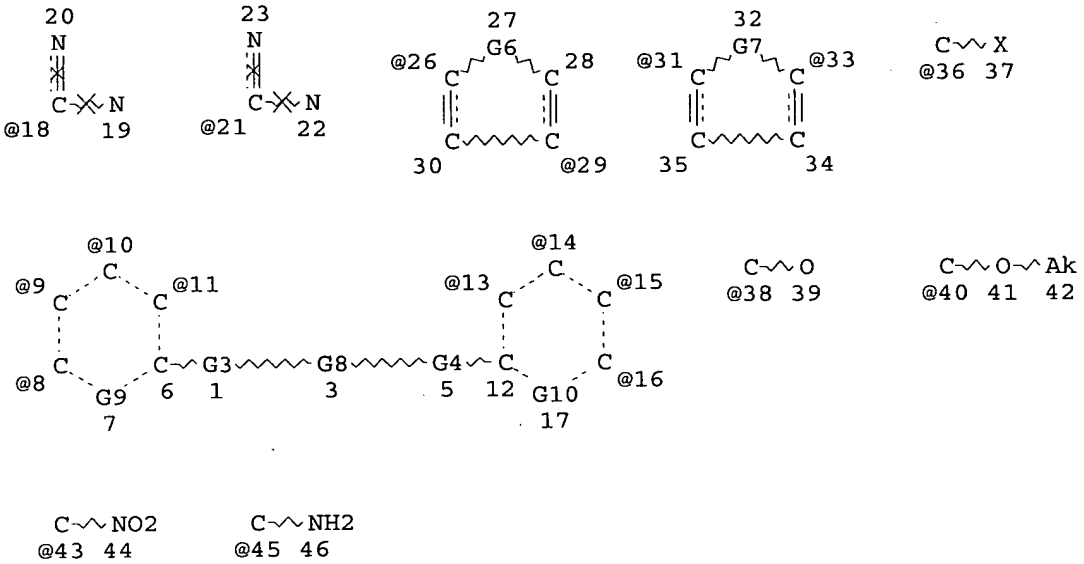
STEREO ATTRIBUTES: NONE
L139(7) SEA FILE=REGISTRY SSS FUL L137
L140(14) SEA FILE=REGISTRY SSS FUL L138
L141(14) SEA FILE=REGISTRY ABB=ON PLU=ON L139 OR L140
L142 STR



REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=26-1 29-5/29-1 26-5/31-1 33-5
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 20
NSPEC IS RC AT 21
NSPEC IS RC AT 22
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 31

STEREO ATTRIBUTES: NONE
L143 STR



```
REP G3=(0-2) CH2
REP G4=(0-2) CH2
VAR G6=O/S/N
VAR G7=O/S/N
VAR G8=26-1 29-5/29-1 26-5/31-1 33-5
VAR G9=CH/36/38/40/43/45
VAR G10=CH/36/38/40/43/45
VPA 18-11/10/9/8 U
VPA 21-13/14/15/16 U
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
NSPEC   IS RC     AT  20
NSPEC   IS RC     AT  21
NSPEC   IS RC     AT  22
NSPEC   IS RC     AT  23
CONNECT IS E1  RC AT  39
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC  12   6
NUMBER OF NODES IS  42

STEREO ATTRIBUTES: NONE
L144             SCR 1841
L145(         86)SEA FILE=REGISTRY SUB=L131 SSS FUL (L144 AND L132 AND L143)
L146(        240)SEA FILE=REGISTRY SSS FUL (L135 AND L143)
L147(          7)SEA FILE=REGISTRY SSS FUL L142
L148(        801)SEA FILE=REGISTRY ABB=ON  PLU=ON  L136 OR L134 OR L141 OR L145
                 OR L146 OR L147
L149(        689)SEA FILE=DRUGU ABB=ON  PLU=ON  L148
L150(     117443)SEA FILE=DRUGU ABB=ON  PLU=ON  COMB./CT
L151(      40082)SEA FILE=DRUGU ABB=ON  PLU=ON  DRUG INTERACTIONS/CC
L152(        107)SEA FILE=DRUGU ABB=ON  PLU=ON  L149 AND (L150 OR L151)
L153(     239769)SEA FILE=DRUGU ABB=ON  PLU=ON  (?NEOPLAS? OR ?CANCER? OR
                 ?CARCIN? OR ?SARCOMA? OR ?LYMPHOM? OR ?MELANOM? OR ?TUMOR? OR
```

```
                ?PROLIFERAT? OR ?LEUKEM? OR ?CHEMOTHERAP? OR ?MYOMA? OR
                ?HODGKIN?)
L154(         12)SEA FILE=DRUGU ABB=ON  PLU=ON  L152 AND L153
L155          12 SEA FILE=DRUGU ABB=ON  PLU=ON  L154 AND L153


=> d que l165
L156(     957195)SEA FILE=WPIX ABB=ON  PLU=ON  (?COMBIN? OR ?SIMULTAN? OR
                ?CONCOMITANT? OR ?INTERACT? OR ?CODRUG? OR ?COADMIN?)/BIX
L157(       3204)SEA FILE=WPIX ABB=ON  PLU=ON  A61K031-496/IPC
L158(        392)SEA FILE=WPIX ABB=ON  PLU=ON  (A61K031-538 OR A61K03105415)/IPC

L159(      24217)SEA FILE=WPIX ABB=ON  PLU=ON  (B06-A02 OR C06-A02 OR B06-D13
                OR C06-D13 OR B06-D16 OR C06-D16 OR B06-E05 OR C06-E05)/MC
L160(      63294)SEA FILE=WPIX ABB=ON  PLU=ON  (B14-H01 OR C14-H01 OR B12-G07
                OR C12-G07)/MC
L161(      24556)SEA FILE=WPIX ABB=ON  PLU=ON  L158 OR L159
L162(        393)SEA FILE=WPIX ABB=ON  PLU=ON  L157 AND L161
L163(        104)SEA FILE=WPIX ABB=ON  PLU=ON  L162 AND L160
L164(         27)SEA FILE=WPIX ABB=ON  PLU=ON  L156 AND L163
L165           7 SEA FILE=WPIX ABB=ON  PLU=ON  L164 AND L158


=> dup rem l33 l61 l94 l130 l155 l165

FILE 'HCAPLUS' ENTERED AT 15:04:26 ON 31 JAN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'MEDLINE' ENTERED AT 15:04:26 ON 31 JAN 2005

FILE 'BIOSIS' ENTERED AT 15:04:26 ON 31 JAN 2005
Copyright (c) 2005 The Thomson Corporation.

FILE 'EMBASE' ENTERED AT 15:04:26 ON 31 JAN 2005
COPYRIGHT (C) 2005 Elsevier Inc. All rights reserved.

FILE 'DRUGU' ENTERED AT 15:04:26 ON 31 JAN 2005
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

FILE 'WPIX' ENTERED AT 15:04:26 ON 31 JAN 2005
COPYRIGHT (C) 2005 THE THOMSON CORPORATION
PROCESSING COMPLETED FOR L33
PROCESSING COMPLETED FOR L61
PROCESSING COMPLETED FOR L94
PROCESSING COMPLETED FOR L130
PROCESSING COMPLETED FOR L155
PROCESSING COMPLETED FOR L165
L181          40 DUP REM L33 L61 L94 L130 L155 L165 (2 DUPLICATES REMOVED)
                ANSWERS '1-11' FROM FILE HCAPLUS
                ANSWERS '12-13' FROM FILE MEDLINE
                ANSWERS '14-15' FROM FILE BIOSIS
                ANSWERS '16-23' FROM FILE EMBASE
                ANSWERS '24-34' FROM FILE DRUGU
                ANSWERS '35-40' FROM FILE WPIX

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 15:04:46 ON 31 JAN 2005
```

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jan 28, 2005 (20050128/UP).

=> d ibib abs ed hitstr 1-11 l181
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, DRUGU, WPIX' -
CONTINUE? (Y)/N:y

L181 ANSWER 1 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:60249 HCAPLUS
DOCUMENT NUMBER: 140:122767
TITLE: Pentamidine compound-chlorpromazine compound combinations for the treatment of **neoplasms**
INVENTOR(S): Borisy, Alexis; Keith, Curtis; Foley, Michael A.; Stockwell, Brent R.; Gaw, Debra A.; Nichols, M. James; Lee, Margaret S.
PATENT ASSIGNEE(S): Combinatorx, Incorporated, USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004006842	A2	20040122	WO 2003-US21803	20030711
WO 2004006842	A3	20040527		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004116407	A1	20040617	US 2003-617424	20030711
PRIORITY APPLN. INFO.:			US 2002-395233P P	20020711
OTHER SOURCE(S):	MARPAT 140:122767			

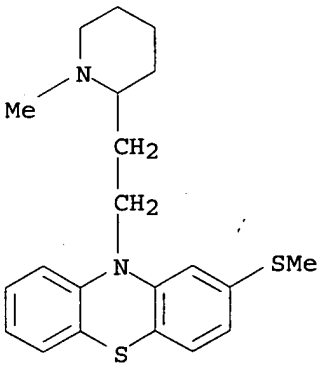
AB The invention features a method for treating a patient having a **cancer** or other **neoplasm** by administering to the patient pentamidine (or an analog thereof) and chlorpromazine (or an analog thereof) simultaneously or within 14 days of each other in amts. sufficient to treat the patient.

ED Entered STN: 26 Jan 2004

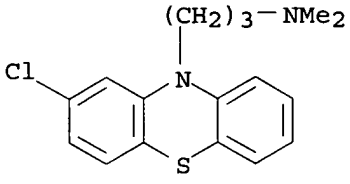
IT **50-52-2**, Thioridazine **50-53-3D**, Chlorpromazine, analogs
58-38-8, Prochlorperazine **58-39-9**, Perphenazine
60-99-1, Methotrimeprazine **61-01-8**, Methoxypromazine
69-23-8, Fluphenazine **84-06-0**, Thiopropazate
100-33-4, Pentamidine **100-33-4D**, Pentamidine, analogs
104-32-5, Propamidine **117-89-5**, Trifluoperazine
146-54-3, Triflupromazine **362-29-8**, Propiomazine
496-00-4, Dibrompropamidine **653-03-2**, Butaperazine

1225-64-5, Norchlorpromazine **1420-55-9**, Thiethylperazine
2095-24-1, Chlorfenethazine **3459-96-9**, Amicarbalide
3546-03-0, Cyamemazine **73819-26-8** **73819-28-0**
80498-71-1 **80498-74-4** **101689-95-6**
124076-61-5, Butamidine **124076-65-9** **166601-05-4**
166601-10-1 **166601-11-2** **173420-56-9**
173420-58-1 **173420-61-6** **173420-63-8**
179118-03-7 **179118-04-8** **179118-05-9**
179118-10-6 **179118-22-0** **190958-06-6**
190958-12-4 **190958-16-8** **216308-16-6**
216308-18-8 **216503-06-9** **242807-42-7**
247032-11-7 **247032-13-9** **247032-15-1**
247032-16-2 **247032-17-3** **247032-18-4**
648415-31-0 **648415-32-1** **648415-36-5**
648415-58-1 **648415-59-2** **648417-90-7**
648417-91-8 **648417-92-9** **648417-93-0**
648417-94-1 **648417-95-2** **648417-96-3**
648417-97-4 **648417-98-5**
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(pentamidine compound-chlorpromazine compound combinations for the treatment of **neoplasms**)

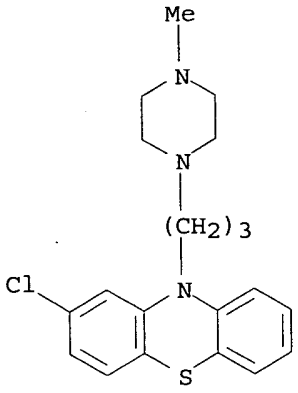
RN 50-52-2 HCAPLUS
CN 10H-Phenothiazine, 10-[2-(1-methyl-2-piperidinyl)ethyl]-2-(methylthio)- (9CI) (CA INDEX NAME)



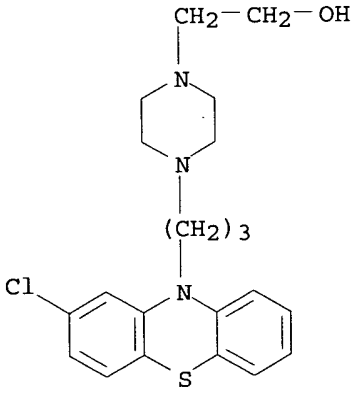
RN 50-53-3 HCAPLUS
CN 10H-Phenothiazine-10-propanamine, 2-chloro-N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 58-38-8 HCAPLUS
CN 10H-Phenothiazine, 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]- (9CI) (CA INDEX NAME)

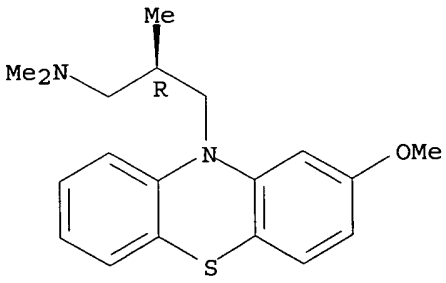


RN 58-39-9 HCAPLUS
CN 1-Piperazineethanol, 4-[3-(2-chloro-10H-phenothiazin-10-yl)propyl]- (9CI) (CA INDEX NAME)

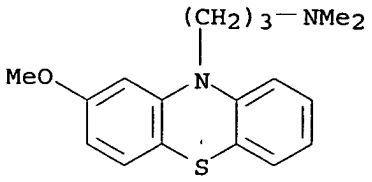


RN 60-99-1 HCAPLUS
CN 10H-Phenothiazine-10-propanamine, 2-methoxy-N,N,β-trimethyl-, (βR)- (9CI) (CA INDEX NAME)

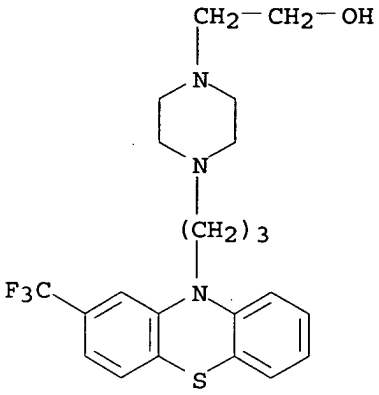
Absolute stereochemistry. Rotation (-).



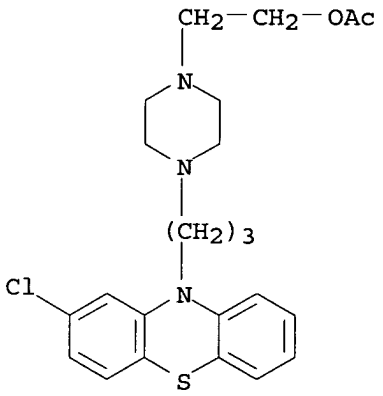
RN 61-01-8 HCAPLUS
CN 10H-Phenothiazine-10-propanamine, 2-methoxy-N,N-dimethyl- (9CI) (CA INDEX NAME)



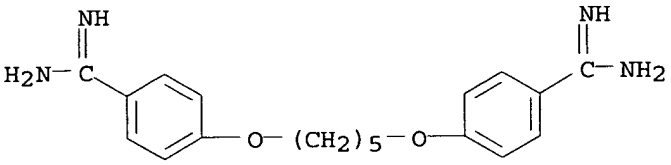
RN 69-23-8 HCAPLUS
CN 1-Piperazineethanol, 4-[3-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]propyl]- (9CI) (CA INDEX NAME)



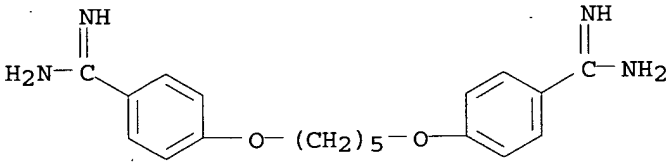
RN 84-06-0 HCAPLUS
CN 1-Piperazineethanol, 4-[3-(2-chloro-10H-phenothiazin-10-yl)propyl]-, acetate (ester) (9CI) (CA INDEX NAME)



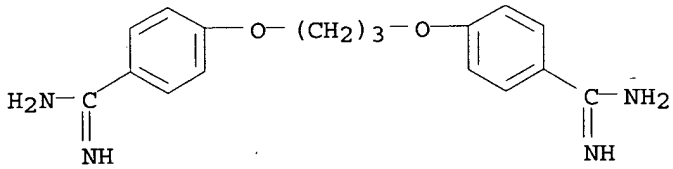
RN 100-33-4 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,5-pentanediylbis(oxy)]bis- (9CI) (CA INDEX NAME)



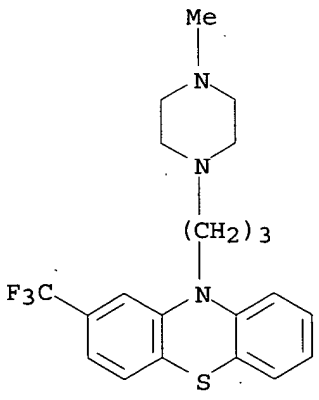
RN 100-33-4 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,5-pentanediylbis(oxy)]bis- (9CI) (CA INDEX NAME)



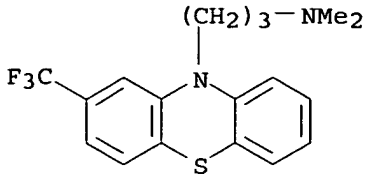
RN 104-32-5 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,3-propanediylbis(oxy)]bis- (9CI) (CA INDEX NAME)



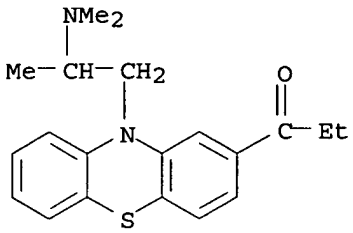
RN 117-89-5 HCAPLUS
CN 10H-Phenothiazine, 10-[3-(4-methyl-1-piperazinyl)propyl]-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



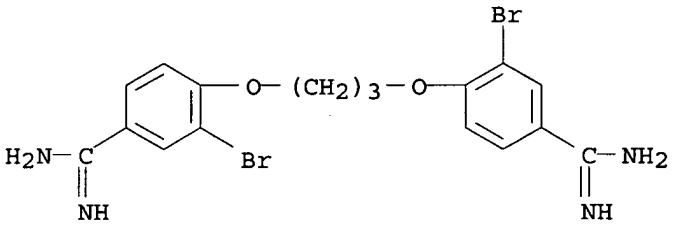
RN 146-54-3 HCAPLUS
CN 10H-Phenothiazine-10-propanamine, N,N-dimethyl-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



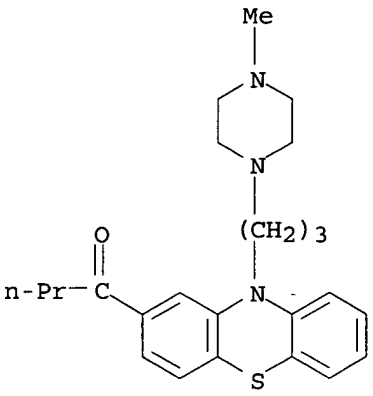
RN 362-29-8 HCAPLUS
CN 1-Propanone, 1-[10-[2-(dimethylamino)propyl]-10H-phenothiazin-2-yl]- (9CI) (CA INDEX NAME)



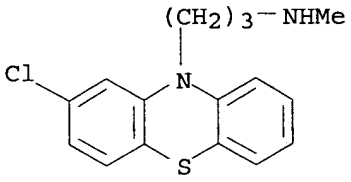
RN 496-00-4 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,3-propanediylbis(oxy)]bis[3-bromo- (9CI) (CA INDEX NAME)



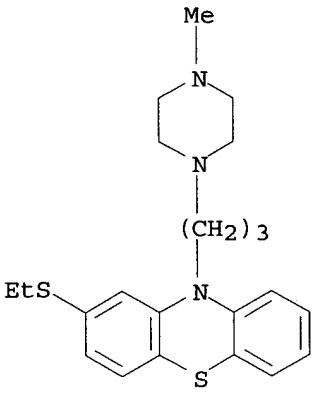
RN 653-03-2 HCAPLUS
CN 1-Butanone, 1-[10-[3-(4-methyl-1-piperazinyl)propyl]-10H-phenothiazin-2-yl]- (9CI) (CA INDEX NAME)



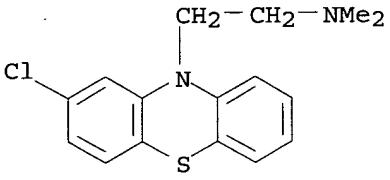
RN 1225-64-5 HCAPLUS
CN 10H-Phenothiazine-10-propanamine, 2-chloro-N-methyl- (9CI) (CA INDEX NAME)



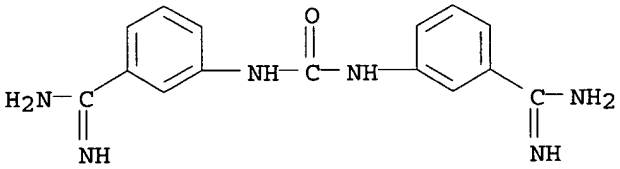
RN 1420-55-9 HCAPLUS
CN 10H-Phenothiazine, 2-(ethylthio)-10-[3-(4-methyl-1-piperazinyl)propyl]- (9CI) (CA INDEX NAME)



RN 2095-24-1 HCAPLUS
CN 10H-Phenothiazine-10-ethanamine, 2-chloro-N,N-dimethyl- (9CI) (CA INDEX NAME)

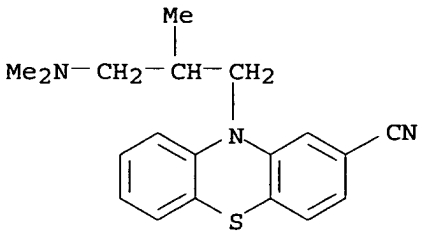


RN 3459-96-9 HCAPLUS
CN Benzenecarboximidamide, 3,3'-(carbonyldiimino)bis- (9CI) (CA INDEX NAME)

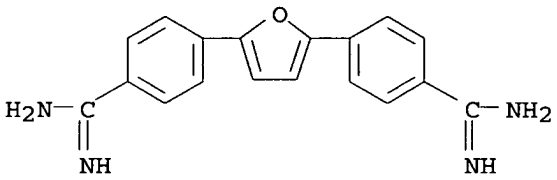


RN 3546-03-0 HCAPLUS

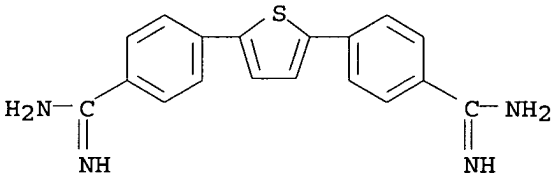
CN 10H-Phenothiazine-2-carbonitrile, 10-[3-(dimethylamino)-2-methylpropyl]- (9CI) (CA INDEX NAME)



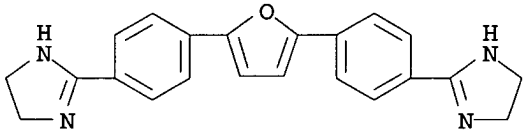
RN 73819-26-8 HCAPLUS
CN Benzenecarboximidamide, 4,4'-(2,5-furandiyl)bis- (9CI) (CA INDEX NAME)



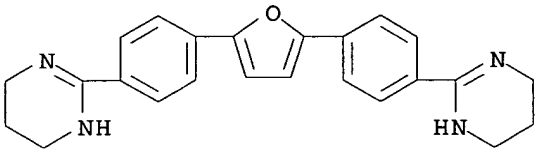
RN 73819-28-0 HCAPLUS
CN Benzenecarboximidamide, 4,4'-(2,5-thiophenediyl)bis- (9CI) (CA INDEX NAME)



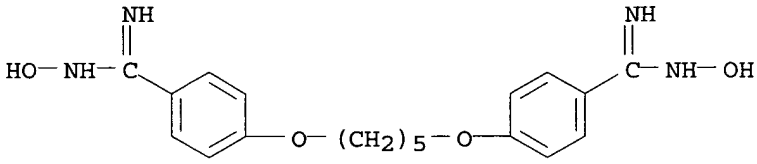
RN 80498-71-1 HCAPLUS
CN 1H-Imidazole, 2,2'-(2,5-furandiyldi-4,1-phenylene)bis[4,5-dihydro- (9CI) (CA INDEX NAME)



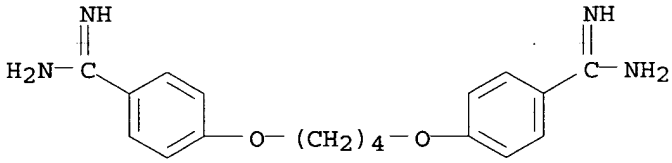
RN 80498-74-4 HCAPLUS
CN Pyrimidine, 2,2'-(2,5-furandiyldi-4,1-phenylene)bis[1,4,5,6-tetrahydro- (9CI) (CA INDEX NAME)



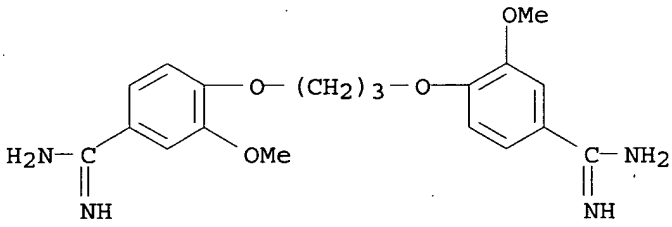
RN 101689-95-6 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,5-pentanediylbis(oxy)]bis[N-hydroxy- (9CI) (CA INDEX NAME)



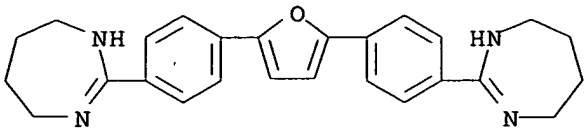
RN 124076-61-5 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,4-butanediylbis(oxy)]bis- (9CI) (CA INDEX NAME)



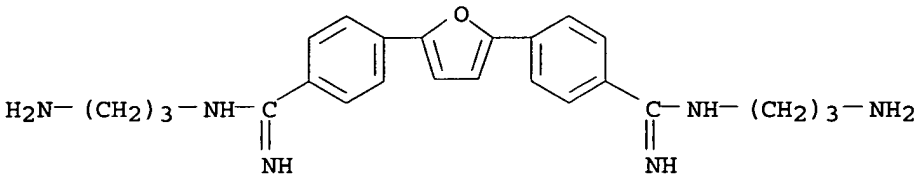
RN 124076-65-9 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,3-propanediylbis(oxy)]bis[3-methoxy- (9CI) (CA INDEX NAME)



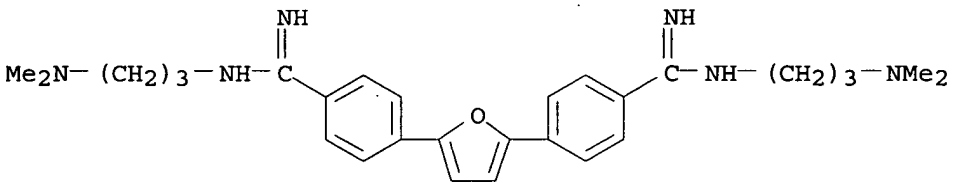
RN 166601-05-4 HCAPLUS
CN 1H-1,3-Diazepine, 2,2'-(2,5-furandiyldi-4,1-phenylene)bis[4,5,6,7-tetrahydro- (9CI) (CA INDEX NAME)



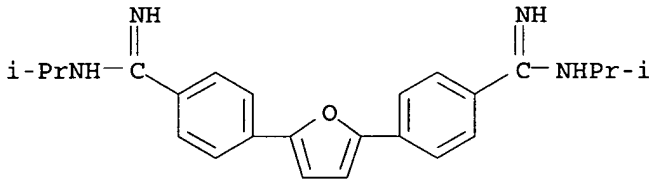
RN 166601-10-1 HCAPLUS
CN Benzenecarboximidamide, 4,4'-(2,5-furandiyl)bis[N-(3-aminopropyl)- (9CI) (CA INDEX NAME)



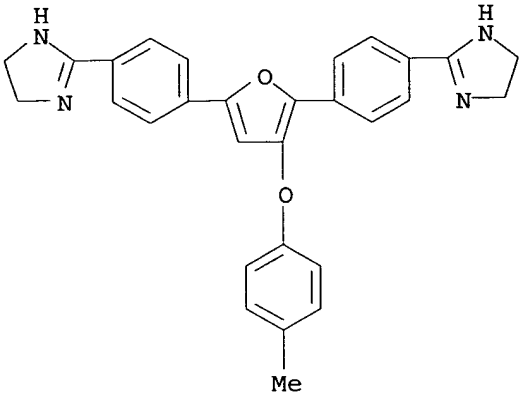
RN 166601-11-2 HCAPLUS
CN Benzenecarboximidamide, 4,4'-(2,5-furandiyl)bis[N-[3-(dimethylamino)propyl]- (9CI) (CA INDEX NAME)



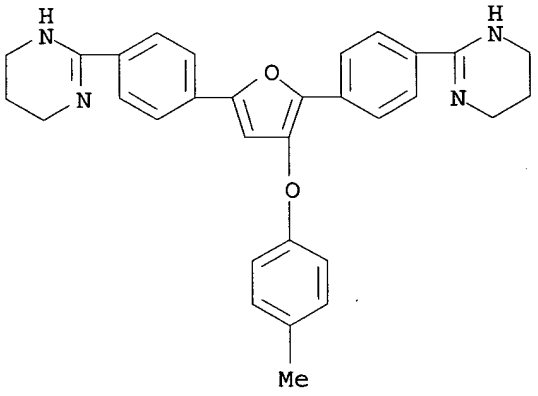
RN 173420-56-9 HCAPLUS
CN Benzenecarboximidamide, 4,4'-(2,5-furandiyl)bis[N-(1-methylethyl)- (9CI) (CA INDEX NAME)



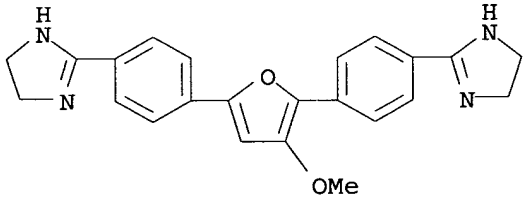
RN 173420-58-1 HCAPLUS
CN 1H-Imidazole, 2,2'-[[3-(4-methylphenoxy)-2,5-furandiyl]di-4,1-phenylene]bis[4,5-dihydro- (9CI) (CA INDEX NAME)



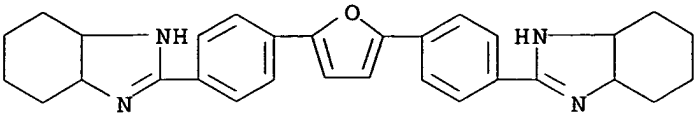
RN 173420-61-6 HCAPLUS
CN Pyrimidine, 2,2'-[[3-(4-methylphenoxy)-2,5-furandiyl]di-4,1-phenylene]bis[1,4,5,6-tetrahydro- (9CI) (CA INDEX NAME)



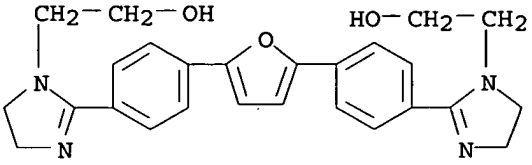
RN 173420-63-8 HCAPLUS
CN 1H-Imidazole, 2,2'-[(3-methoxy-2,5-furandiyl)di-4,1-phenylene]bis[4,5-dihydro- (9CI) (CA INDEX NAME)



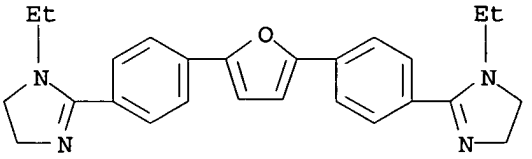
RN 179118-03-7 HCAPLUS
CN 1H-Benzimidazole, 2,2'-(2,5-furandiyldi-4,1-phenylene)bis[3a,4,5,6,7,7a-hexahydro- (9CI) (CA INDEX NAME)



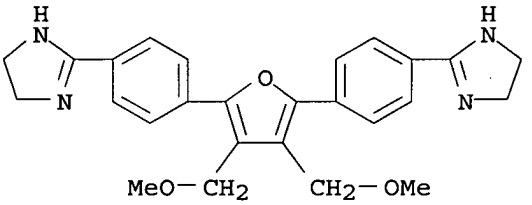
RN 179118-04-8 HCAPLUS
CN 1H-Imidazole-1-ethanol, 2,2'-(2,5-furandiyldi-4,1-phenylene)bis[4,5-dihydro- (9CI) (CA INDEX NAME)



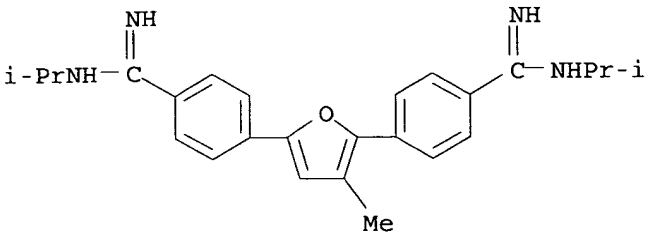
RN 179118-05-9 HCAPLUS
CN 1H-Imidazole, 2,2'-(2,5-furandiyldi-4,1-phenylene)bis[1-ethyl-4,5-dihydro- (9CI) (CA INDEX NAME)



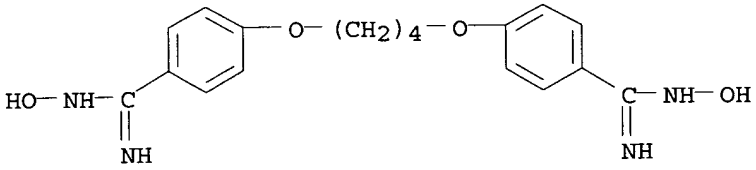
RN 179118-10-6 HCAPLUS
CN 1H-Imidazole, 2,2'-[[3,4-bis(methoxymethyl)-2,5-furandiyl]di-4,1-phenylene]bis[4,5-dihydro- (9CI) (CA INDEX NAME)



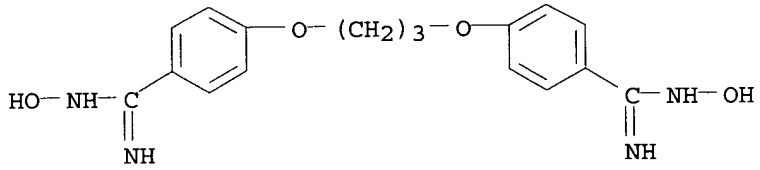
RN 179118-22-0 HCAPLUS
CN Benzenecarboximidamide, 4,4'-(3-methyl-2,5-furandiyl)bis[N-(1-methylethyl)- (9CI) (CA INDEX NAME)



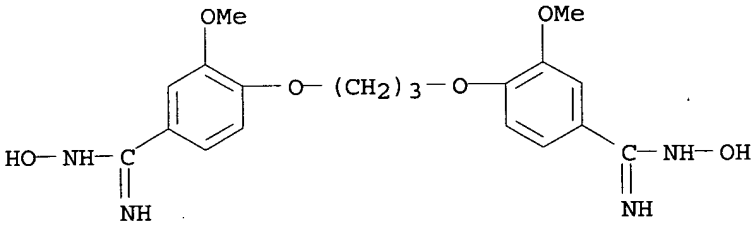
RN 190958-06-6 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,4-butanediylbis(oxy)]bis[N-hydroxy- (9CI) (CA INDEX NAME)



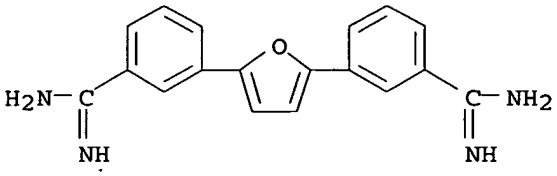
RN 190958-12-4 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,3-propanediylbis(oxy)]bis[N-hydroxy- (9CI) (CA INDEX NAME)



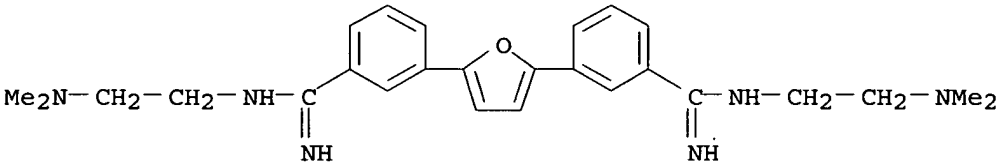
RN 190958-16-8 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,3-propanediylbis(oxy)]bis[N-hydroxy-3-methoxy- (9CI) (CA INDEX NAME)



RN 216308-16-6 HCAPLUS
CN Benzenecarboximidamide, 3,3'-(2,5-furandiyl)bis- (9CI) (CA INDEX NAME)

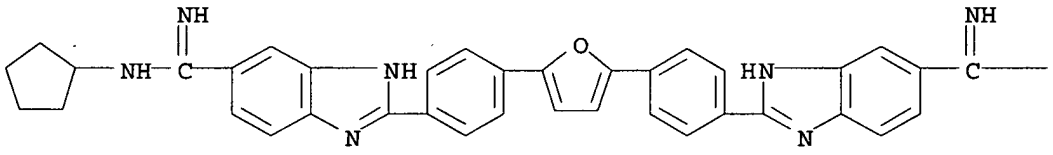


RN 216308-18-8 HCAPLUS
CN Benzenecarboximidamide, 3,3'-(2,5-furandiyl)bis[N-[2-(dimethylamino)ethyl]- (9CI) (CA INDEX NAME)

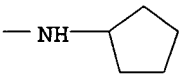


RN 216503-06-9 HCAPLUS
CN 1H-Benzimidazole-5-carboximidamide, 2,2'-(2,5-furandiyldi-4,1-phenylene)bis[N-cyclopentyl- (9CI) (CA INDEX NAME)

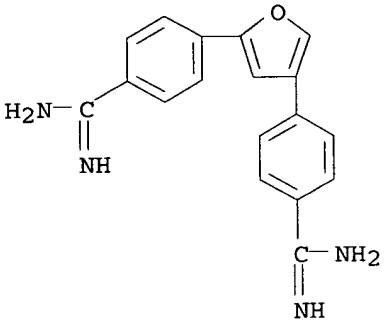
PAGE 1-A



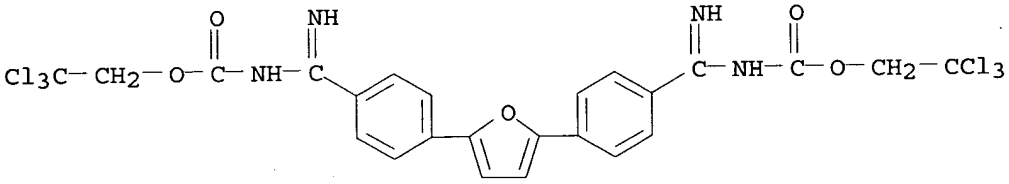
PAGE 1-B



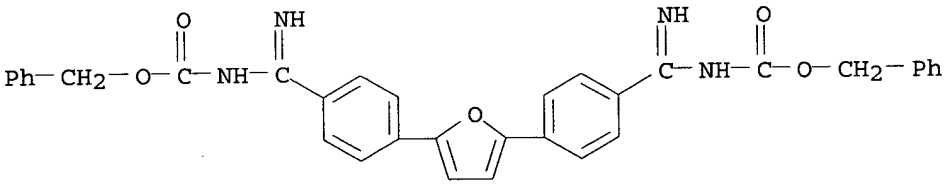
RN 242807-42-7 HCAPLUS
CN Benzenecarboximidamide, 4,4'-(2,4-furandiyl)bis- (9CI) (CA INDEX NAME)



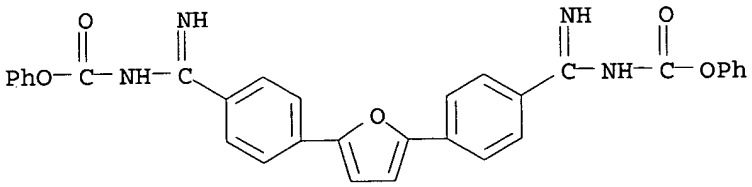
RN 247032-11-7 HCAPLUS
CN Carbamic acid, [2,5-furandiylbis(4,1-phenylenecarbonimidoyl)]bis-, bis(2,2,2-trichloroethyl) ester (9CI) (CA INDEX NAME)



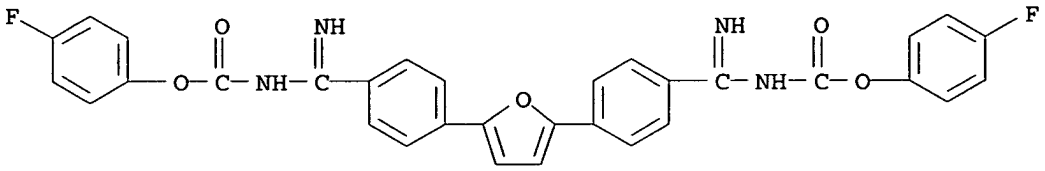
RN 247032-13-9 HCAPLUS
CN Carbamic acid, [2,5-furandiylbis(4,1-phenylenecarbonimidoyl)]bis-, bis(phenylmethyl) ester (9CI) (CA INDEX NAME)



RN 247032-15-1 HCAPLUS
CN Carbamic acid, [2,5-furandiylbis(4,1-phenylenecarbonimidoyl)]bis-, diphenyl ester (9CI) (CA INDEX NAME)

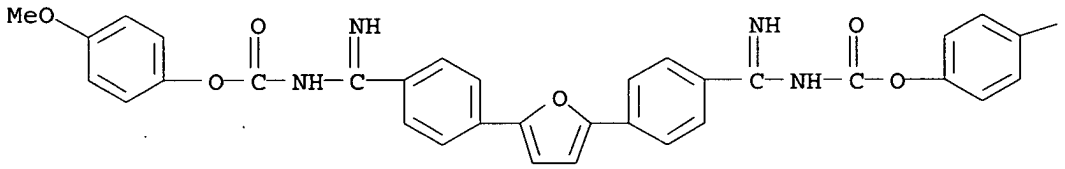


RN 247032-16-2 HCAPLUS
CN Carbamic acid, [2,5-furandiylbis(4,1-phenylenecarbonimidoyl)]bis-, bis(4-fluorophenyl) ester (9CI) (CA INDEX NAME)



RN 247032-17-3 HCAPLUS
CN Carbamic acid, [2,5-furandiylbis(4,1-phenylenecarbonimidoyl)]bis-, bis(4-methoxyphenyl) ester (9CI) (CA INDEX NAME)

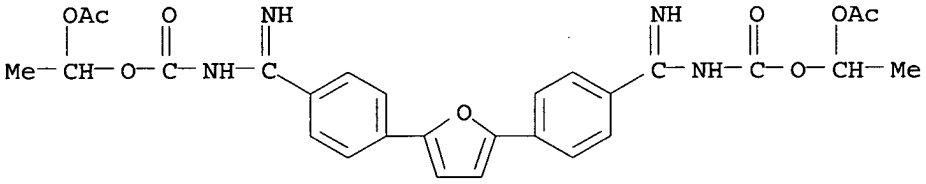
PAGE 1-A



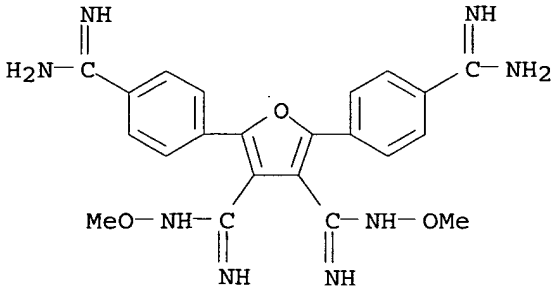
PAGE 1-B

OMe

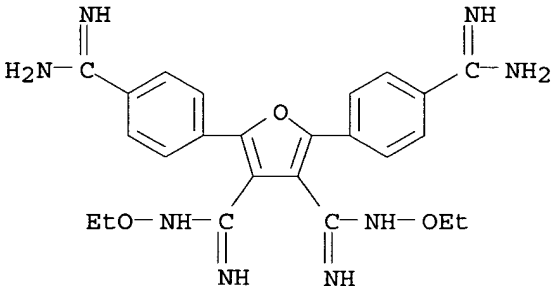
RN 247032-18-4 HCAPLUS
CN Carbamic acid, [2,5-furandiylbis(4,1-phenylenecarbonimidoyl)]bis-, bis[1-(acetyloxy)ethyl] ester (9CI) (CA INDEX NAME)



RN 648415-31-0 HCAPLUS
CN 3,4-Furandicarboximidamide, 2,5-bis[4-(aminoiminomethyl)phenyl]-N,N''-dimethoxy- (9CI) (CA INDEX NAME)

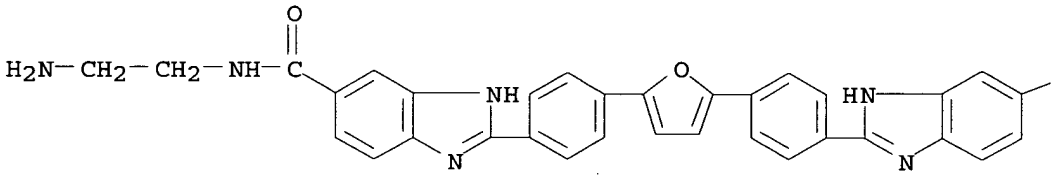


RN 648415-32-1 HCAPLUS
CN 3,4-Furandicarboximidamide, 2,5-bis[4-(aminoiminomethyl)phenyl]-N,N''-diethoxy- (9CI) (CA INDEX NAME)

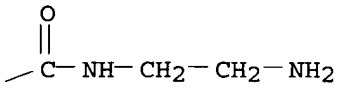


RN 648415-36-5 HCAPLUS
CN 1H-Benzimidazole-5-carboxamide, 2,2'-(2,5-furandiyldi-4,1-phenylene)bis[N-(2-aminoethyl)- (9CI) (CA INDEX NAME)

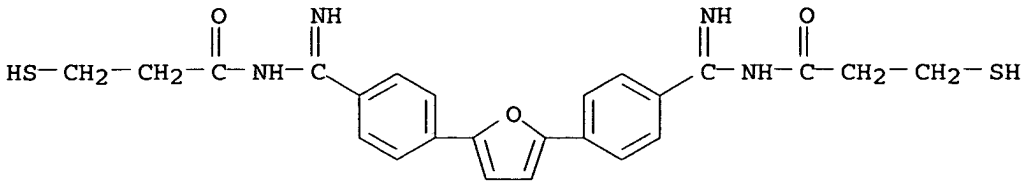
PAGE 1-A



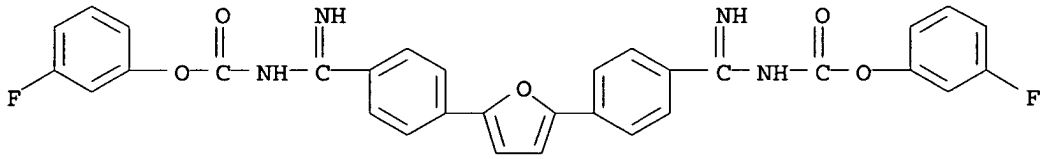
PAGE 1-B



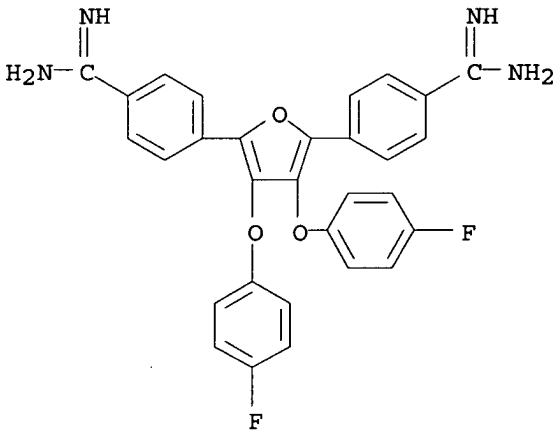
RN 648415-58-1 HCAPLUS
CN Propanamide, N,N'-[2,5-furandiylbis(4,1-phenylenecarbonimidoyl)]bis[3-mercapto- (9CI) (CA INDEX NAME)



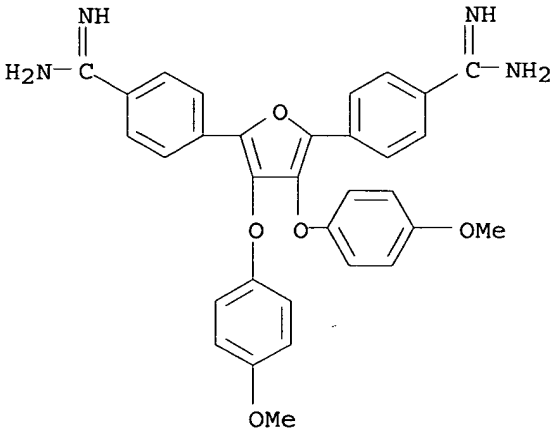
RN 648415-59-2 HCAPLUS
CN Carbamic acid, [2,5-furandiylbis(4,1-phenylenecarbonimidoyl)]bis-, bis(3-fluorophenyl) ester (9CI) (CA INDEX NAME)



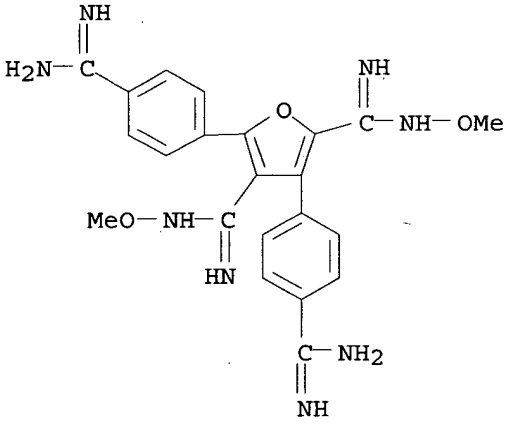
RN 648417-90-7 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[3,4-bis(4-fluorophenoxy)-2,5-furandiyl]bis- (9CI) (CA INDEX NAME)



RN 648417-91-8 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[3,4-bis(4-methoxyphenoxy)-2,5-furandiyl]bis- (9CI) (CA INDEX NAME)

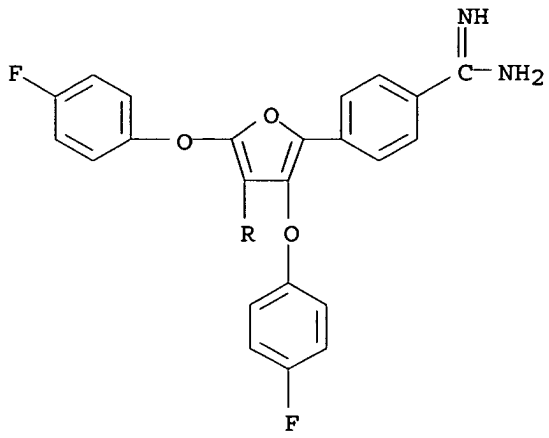


RN 648417-92-9 HCAPLUS
CN 2,4-Furandicarboximidamide, 3,5-bis[4-(aminoiminomethyl)phenyl]-N,N''-dimethoxy- (9CI) (CA INDEX NAME)

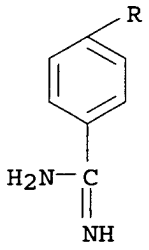


RN 648417-93-0 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[3,5-bis(4-fluorophenoxy)-2,4-furandiyl]bis- (9CI) (CA INDEX NAME)

PAGE 1-A

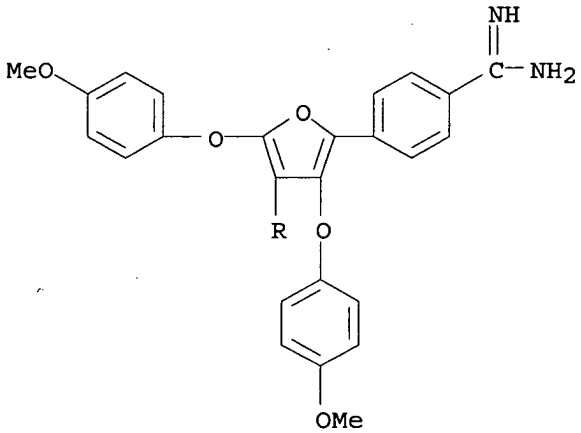


PAGE 2-A

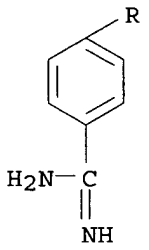


RN 648417-94-1 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[3,5-bis(4-methoxyphenoxy)-2,4-furandiyl]bis- (9CI) (CA INDEX NAME)

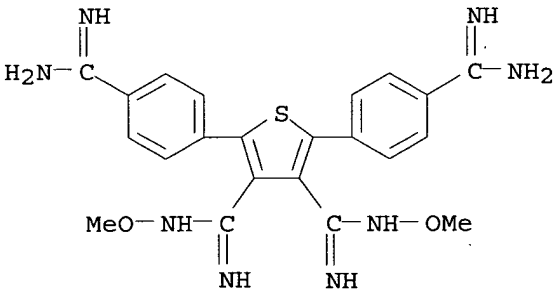
PAGE 1-A



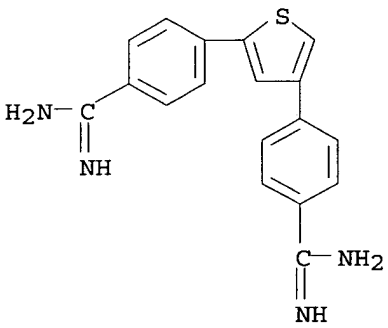
PAGE 2-A



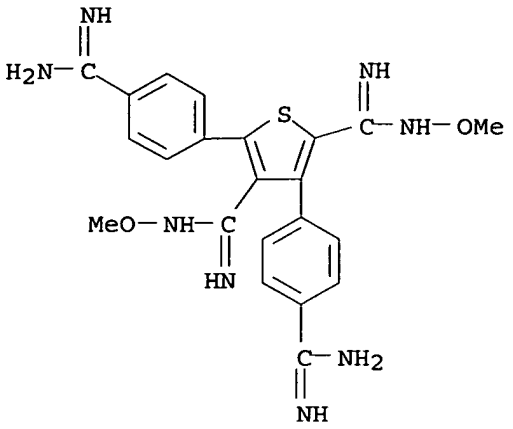
RN 648417-95-2 HCAPLUS
CN 3,4-Thiophenedicarboximidamide, 2,5-bis[4-(aminoiminomethyl)phenyl]-N,N''-dimethoxy- (9CI) (CA INDEX NAME)



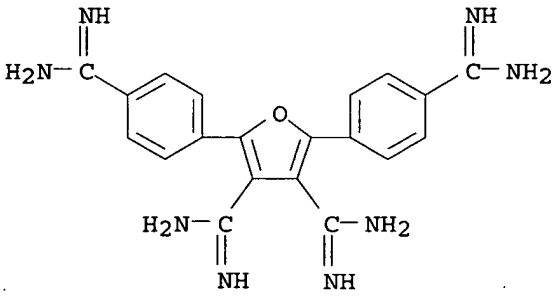
RN 648417-96-3 HCAPLUS
CN Benzenecarboximidamide, 4,4'-(2,4-thiophenediyl)bis- (9CI) (CA INDEX NAME)



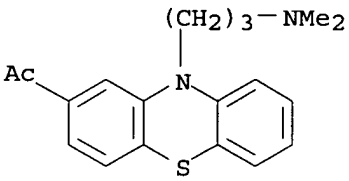
RN 648417-97-4 HCAPLUS
CN 2,4-Thiophenedicarboximidamide, 3,5-bis[4-(aminoiminomethyl)phenyl]-N,N''-dimethoxy- (9CI) (CA INDEX NAME)



RN 648417-98-5 HCAPLUS
CN 3,4-Furandicarboximidamide, 2,5-bis[4-(aminoiminomethyl)phenyl]- (9CI) (CA INDEX NAME)



IT **61-00-7**, Acepromazine
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(pentamidine compound-chlorpromazine compound combinations for treatment of **neoplasms**)
RN 61-00-7 HCAPLUS
CN Ethanone, 1-[10-[3-(dimethylamino)propyl]-10H-phenothiazin-2-yl]- (9CI) (CA INDEX NAME)



L181 ANSWER 2 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:698121 HCAPLUS
DOCUMENT NUMBER: 141:218970
TITLE: Method and composition for potentiating an opiate analgesic
INVENTOR(S): Wang, Zaijie

PATENT ASSIGNEE(S): The Board of Trustees of the University of Illinois, USA
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004071413	A2	20040826	WO 2004-US2951	20040203
WO 2004071413	A3	20041209		

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004220203	A1	20041104	US 2004-769536	20040130

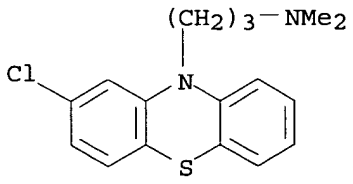
PRIORITY APPLN. INFO.: US 2003-446232P P 20030210

AB Composition and methods of treating pain and reducing, reversing, or preventing tolerance to opiate analgesics are disclosed. The composition and method utilize an opiate analgesic and a calcium calmodulin kinase (CaMKII) inhibitor as active agents to treat pain in mammals, including humans.

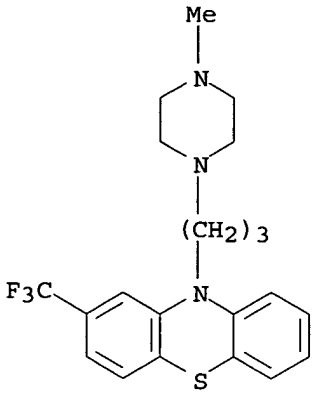
ED Entered STN: 26 Aug 2004

IT **50-53-3**, Chlorpromazine, biological studies **117-89-5**, Trifluoperazine **140-64-7**, Pentamidine isethionate **3892-78-2**
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(method and composition for potentiating an opiate analgesic using calcium calmodulin kinase CaMKII inhibitor in relation to preventing dependence and tolerance and treating withdrawal)

RN 50-53-3 HCAPLUS
CN 10H-Phenothiazine-10-propanamine, 2-chloro-N,N-dimethyl- (9CI) (CA INDEX NAME)



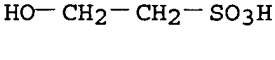
RN 117-89-5 HCAPLUS
CN 10H-Phenothiazine, 10-[3-(4-methyl-1-piperazinyl)propyl]-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



RN 140-64-7 HCAPLUS
CN Ethanesulfonic acid, 2-hydroxy-, compd. with 4,4'-[1,5-pentanediylbis(oxy)]bis[benzenecarboximidamide] (2:1) (9CI) (CA INDEX NAME)

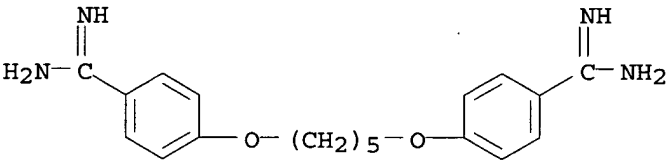
CM 1

CRN 107-36-8
CMF C2 H6 O4 S

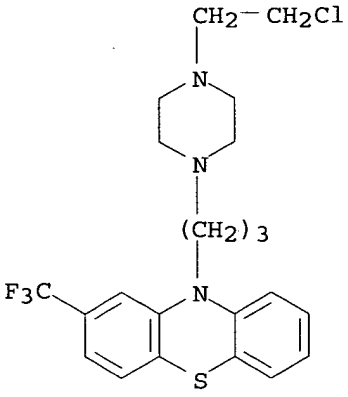


CM 2

CRN 100-33-4
CMF C19 H24 N4 O2



RN 3892-78-2 HCAPLUS
CN 10H-Phenothiazine, 10-[3-[4-(2-chloroethyl)-1-piperazinyl]propyl]-2-(trifluoromethyl)-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L181 ANSWER 3 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:81936 HCAPLUS
DOCUMENT NUMBER: 140:228344
TITLE: Discovering modes of action for therapeutic compounds using a genome-wide screen of yeast heterozygotes
AUTHOR(S): Lum, Pek Yee; Armour, Christopher D.; Stepaniants, Sergey B.; Cavet, Guy; Wolf, Maria K.; Butler, J. Scott; Hinshaw, Jerald C.; Garnier, Philippe; Prestwich, Glenn D.; Leonardson, Amy; Garrett-Engele, Philip; Rush, Christopher M.; Bard, Martin; Schimmack, Greg; Phillips, John W.; Roberts, Christopher J.; Shoemaker, Daniel D.
CORPORATE SOURCE: Rosetta Inpharmatics LLC, Kirkland, WA, 98034, USA
SOURCE: Cell (Cambridge, MA, United States) (2004), 116(1), 121-137
CODEN: CELLB5; ISSN: 0092-8674
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

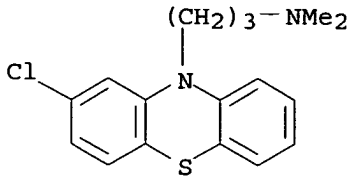
AB Modern medicine faces the challenge of developing safer and more effective therapies to treat human diseases. Many drugs currently in use were discovered without knowledge of their underlying mol. mechanisms. Understanding their biol. targets and modes of action will be essential to design improved second-generation compds. Here, we describe the use of a genome-wide pool of tagged heterozygotes to assess the cellular effects of 78 compds. in Saccharomyces cerevisiae. Specifically, lanosterol synthase in the sterol biosynthetic pathway was identified as a target of the antianginal drug molsidomine, which may explain its cholesterol-lowering effects. Further, the rRNA processing exosome was identified as a potential target of the cell growth inhibitor 5-fluorouracil. This genome-wide screen validated previously characterized targets or helped identify potentially new modes of action for over half of the compds. tested, providing proof of this principle for analyzing the modes of action of clin. relevant compds.

ED Entered STN: 02 Feb 2004
IT **50-53-3**, biological studies **100-33-4 117-89-5**
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)

(discovering modes of action for therapeutic compds. using a genome-wide screen of yeast heterozygotes)

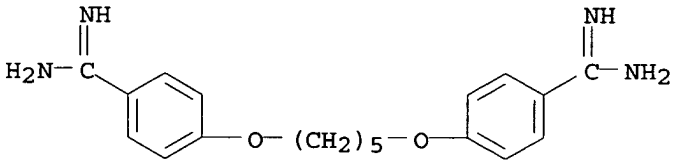
RN 50-53-3 HCAPLUS

CN 10H-Phenothiazine-10-propanamine, 2-chloro-N,N-dimethyl- (9CI) (CA INDEX NAME)



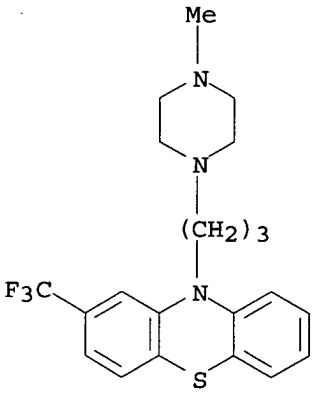
RN 100-33-4 HCAPLUS

CN Benzenecarboximidamide, 4,4'-[1,5-pentanediylbis(oxy)]bis- (9CI) (CA INDEX NAME)



RN 117-89-5 HCAPLUS

CN 10H-Phenothiazine, 10-[3-(4-methyl-1-piperazinyl)propyl]-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L181 ANSWER 4 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:334927 HCAPLUS

DOCUMENT NUMBER: 138:314640

TITLE: Use of histamine and histamine agonists to treat liver disease

INVENTOR(S): Gehlsen, Kurt R.; Haaparanta, Tapio S. K.; Hornyak, Stephen C.

PATENT ASSIGNEE(S): Maxim Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003035095	A1	20030501	WO 2002-US32675	20021011
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003091553	A1	20030515	US 2002-270713	20021011
EP 1435984	A1	20040714	EP 2002-802137	20021011
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

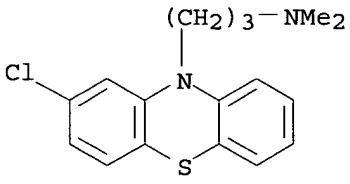
PRIORITY APPLN. INFO.:		
US 2001-343628P	P	20011019
US 2001-340011P	P	20011030
WO 2002-US32675	W	20021011

AB Methods are provided for treating and/or preventing hepatic tissue and cell damage caused by reactive oxygen species in mammals. More specifically, the invention discloses the prevention and/or reduction of hepatic tissue and cell damage through the administration of histamine and histamine agonists.

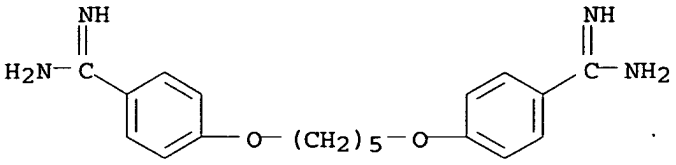
ED Entered STN: 02 May 2003

IT **50-53-3**, Chlorpromazine, biological studies **100-33-4**, Pentamidine
RL: **ADV (Adverse effect, including toxicity); BIOL (Biological study)**
(hepatotoxic drug; histamine and histamine agonists to treat liver disease)

RN 50-53-3 HCAPLUS
CN 10H-Phenothiazine-10-propanamine, 2-chloro-N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 100-33-4 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,5-pentanediylbis(oxy)]bis- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L181 ANSWER 5 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:574914 HCAPLUS
DOCUMENT NUMBER: 137:119653
TITLE: Combinations of drugs (e.g., chlorpromazine and pentamidine) for the treatment of **neoplastic** disorders
INVENTOR(S): Borisy, Alexis; Keith, Curtis; Foley, Michael A.; Stockwell, Brent R.
PATENT ASSIGNEE(S): Combinatorx, Incorporated, USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002058684	A2	20020801	WO 2001-US47959	20011030
WO 2002058684	A3	20030417		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 6569853	B1	20030527	US 2000-706929	20001106
CA 2436799	AA	20020801	CA 2001-2436799	20011030
EE 200300212	A	20030815	EE 2003-212	20011030
EP 1339399	A2	20030903	EP 2001-994213	20011030
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001015166	A	20031230	BR 2001-15166	20011030
JP 2004517915	T2	20040617	JP 2002-559018	20011030
US 2003166642	A1	20030904	US 2003-347714	20030121
US 6846816	B2	20050125		
NO 2003002036	A	20030704	NO 2003-2036	20030506
BG 107831	A	20040227	BG 2003-107831	20030520
PRIORITY APPLN. INFO.:			US 2000-706929	A1 20001106
			WO 2001-US47959	W 20011030

OTHER SOURCE(S): MARPAT 137:119653
AB The invention features a method for treating a patient having a **cancer** or other **neoplasm**, by administering to the patient (i) chlorpromazine or a metabolite or analog thereof; and (ii)

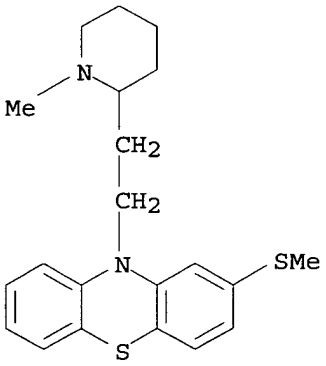
pentamidine or a metabolite or analog thereof simultaneously or within 14 days of each other in amts. sufficient to inhibit the growth of the **neoplasm.**

ED Entered STN: 02 Aug 2002

IT **50-52-2**, Thioridazine **50-53-3**, Chlorpromazine, biological studies **58-38-8**, Prochlorperazine **58-39-9**, Perphenazine **60-99-1**, Methotrimeprazine **61-00-7**, Acepromazine **61-01-8**, Methopromazine **84-06-0**, Thiopropazate **100-33-4**, Pentamidine **104-32-5**, Propamidine **117-89-5**, Trifluoperazine **140-64-7**, Pentamidine isethionate **362-29-8**, Propiomazine **496-00-4**, Dibromopropamidine **653-03-2**, Butaperazine **1225-64-5**, Norchlorpromazine **1420-55-9**, Thiethylperazine **2095-24-1**, Chlorfenethazine **3459-96-9**, Amicarbalide **3546-03-0**, Cyamemazine **17528-28-8**, Perphenazine enanthate **124076-61-5**, Butamidine **124076-65-9**
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(drug combinations for treatment of **neoplastic** disorders)

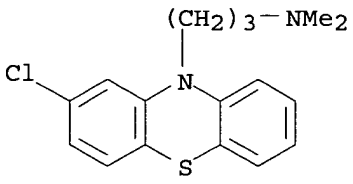
RN 50-52-2 HCAPLUS

CN 10H-Phenothiazine, 10-[2-(1-methyl-2-piperidinyl)ethyl]-2-(methylthio)- (9CI) (CA INDEX NAME)



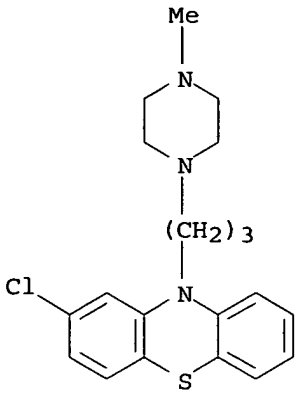
RN 50-53-3 HCAPLUS

CN 10H-Phenothiazine-10-propanamine, 2-chloro-N,N-dimethyl- (9CI) (CA INDEX NAME)

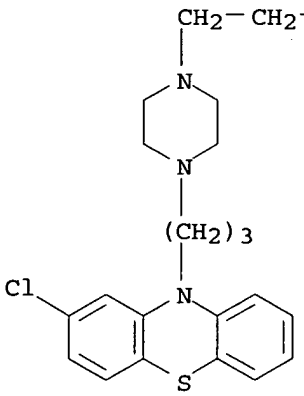


RN 58-38-8 HCAPLUS

CN 10H-Phenothiazine, 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]- (9CI) (CA INDEX NAME)

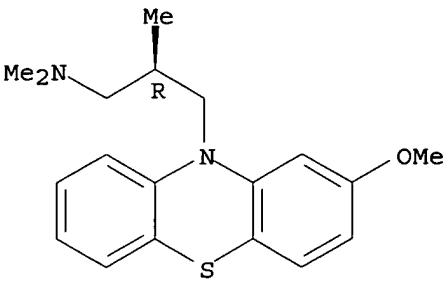


RN 58-39-9 HCAPLUS
CN 1-Piperazineethanol, 4-[3-(2-chloro-10H-phenothiazin-10-yl)propyl]- (9CI) (CA INDEX NAME)

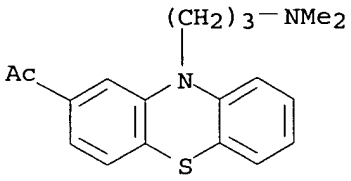


RN 60-99-1 HCAPLUS
CN 10H-Phenothiazine-10-propanamine, 2-methoxy-N,N,β-trimethyl-, (βR)- (9CI) (CA INDEX NAME)

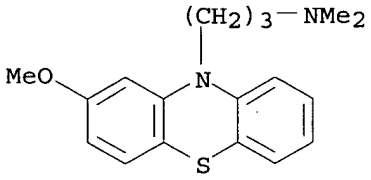
Absolute stereochemistry. Rotation (-).



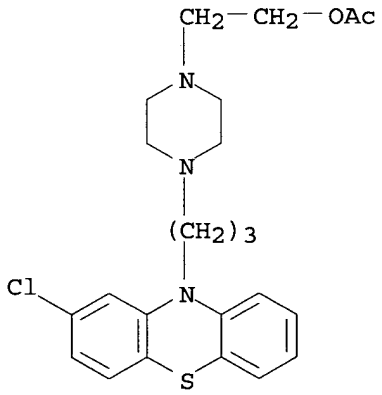
RN 61-00-7 HCAPLUS
CN Ethanone, 1-[10-[3-(dimethylamino)propyl]-10H-phenothiazin-2-yl]- (9CI) (CA INDEX NAME)



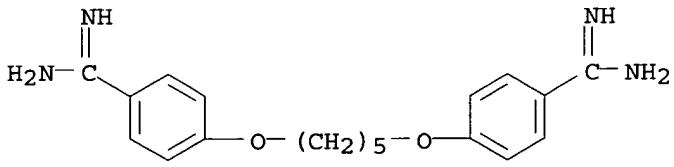
RN 61-01-8 HCAPLUS
CN 10H-Phenothiazine-10-propanamine, 2-methoxy-N,N-dimethyl- (9CI) (CA INDEX NAME)



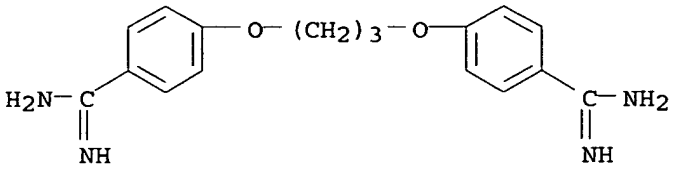
RN 84-06-0 HCAPLUS
CN 1-Piperazineethanol, 4-[3-(2-chloro-10H-phenothiazin-10-yl)propyl]-, acetate (ester) (9CI) (CA INDEX NAME)



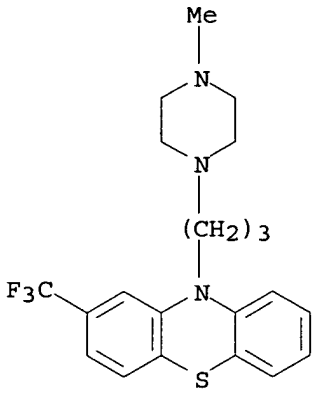
RN 100-33-4 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,5-pentanediylbis(oxy)]bis- (9CI) (CA INDEX NAME)



RN 104-32-5 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,3-propanediylbis(oxy)]bis- (9CI) (CA INDEX NAME)



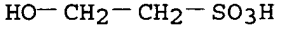
RN 117-89-5 HCAPLUS
CN 10H-Phenothiazine, 10-[3-(4-methyl-1-piperazinyl)propyl]-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



RN 140-64-7 HCAPLUS
CN Ethanesulfonic acid, 2-hydroxy-, compd. with 4,4'-[1,5-pentanediylbis(oxy)]bis[benzenecarboximidamide] (2:1) (9CI) (CA INDEX NAME)

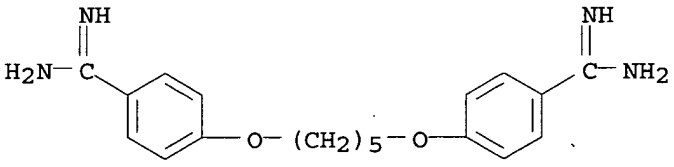
CM 1

CRN 107-36-8
CMF C2 H6 O4 S



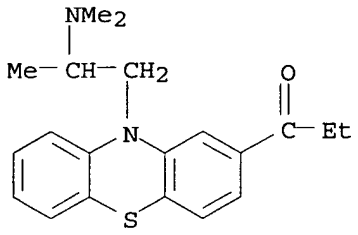
CM 2

CRN 100-33-4
CMF C19 H24 N4 O2

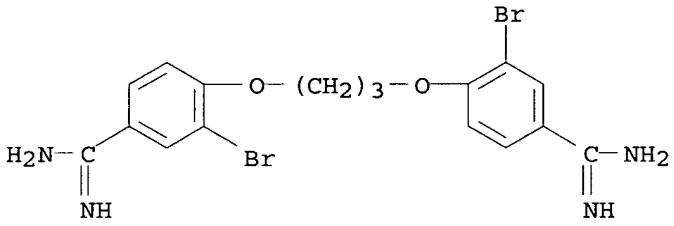


RN 362-29-8 HCAPLUS

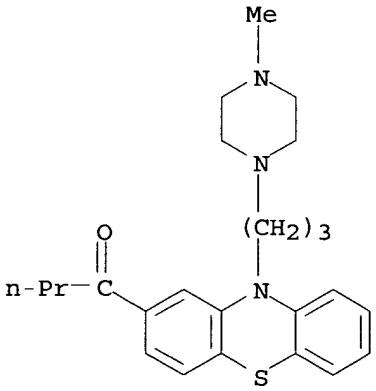
CN 1-Propanone, 1-[10-[2-(dimethylamino)propyl]-10H-phenothiazin-2-yl]- (9CI) (CA INDEX NAME)



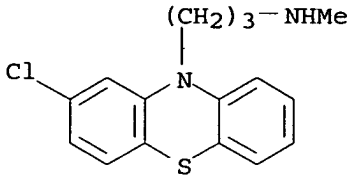
RN 496-00-4 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,3-propanediylbis(oxy)]bis[3-bromo- (9CI) (CA INDEX NAME)



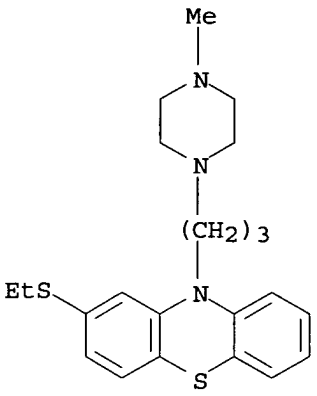
RN 653-03-2 HCAPLUS
CN 1-Butanone, 1-[10-[3-(4-methyl-1-piperazinyl)propyl]-10H-phenothiazin-2-yl]- (9CI) (CA INDEX NAME)



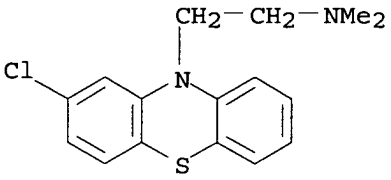
RN 1225-64-5 HCAPLUS
CN 10H-Phenothiazine-10-propanamine, 2-chloro-N-methyl- (9CI) (CA INDEX NAME)



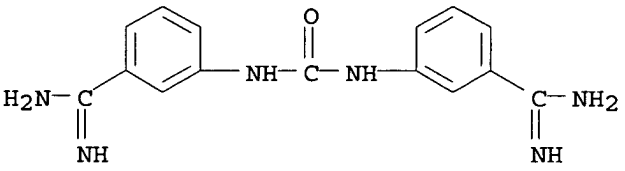
RN 1420-55-9 HCAPLUS
CN 10H-Phenothiazine, 2-(ethylthio)-10-[3-(4-methyl-1-piperazinyl)propyl]-(9CI) (CA INDEX NAME)



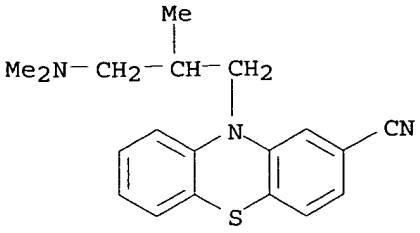
RN 2095-24-1 HCAPLUS
CN 10H-Phenothiazine-10-ethanamine, 2-chloro-N,N-dimethyl- (9CI) (CA INDEX NAME)



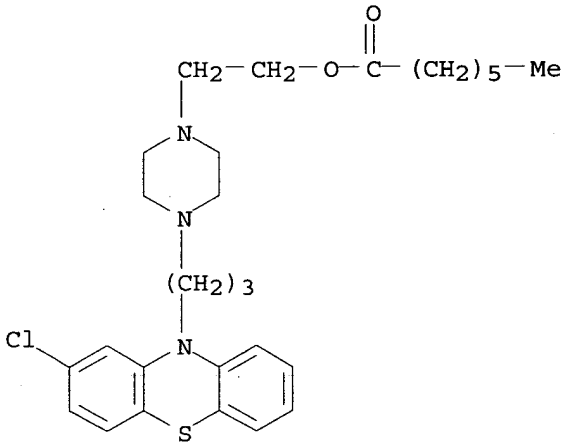
RN 3459-96-9 HCAPLUS
CN Benzenecarboximidamide, 3,3'-(carbonyldiimino)bis- (9CI) (CA INDEX NAME)



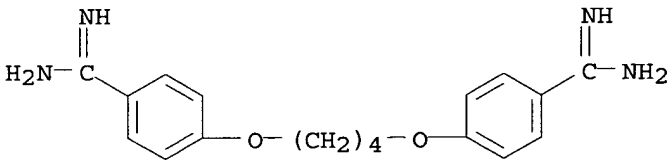
RN 3546-03-0 HCAPLUS
CN 10H-Phenothiazine-2-carbonitrile, 10-[3-(dimethylamino)-2-methylpropyl]-(9CI) (CA INDEX NAME)



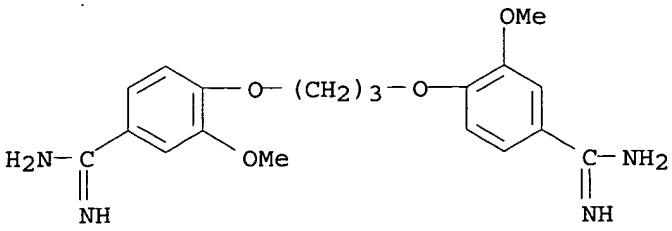
RN 17528-28-8 HCAPLUS
CN Heptanoic acid, 2-[4-[3-(2-chloro-10H-phenothiazin-10-yl)propyl]-1-piperazinyl]ethyl ester (9CI) (CA INDEX NAME)



RN 124076-61-5 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,4-butanediylbis(oxy)]bis- (9CI) (CA INDEX NAME)



RN 124076-65-9 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,3-propanediylbis(oxy)]bis[3-methoxy- (9CI) (CA INDEX NAME)



L181 ANSWER 6 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:338762 HCAPLUS
DOCUMENT NUMBER: 134:362292
TITLE: Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile
INVENTOR(S): Farr, Spencer
PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA
SOURCE: PCT Int. Appl., 222 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032928	A2	20010510	WO 2000-US30474	20001103
WO 2001032928	A3	20020725		

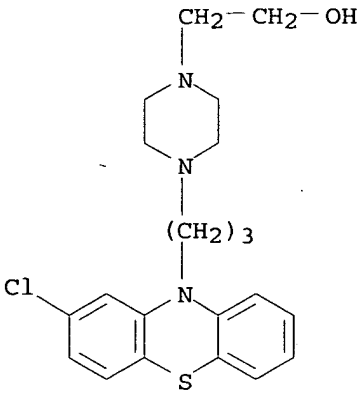
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-165398P P 19991105
US 2000-196571P P 20000411

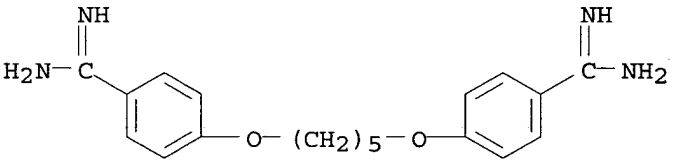
AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to determine the hypersensitivity of individuals to a given agent, such as drug or other chemical, in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes associated with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes associated with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes associated with hypersensitivity. The expression of the genes predetd. to be associated with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and apparatus useful for identifying hypersensitivity in a subject are also disclosed.

ED Entered STN: 11 May 2001
IT **58-39-9**, Perphenazine **100-33-4**, Pentamidine
RL: **BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)**
(methods of determining individual hypersensitivity to a pharmaceutical agent
from gene expression profile)
RN 58-39-9 HCAPLUS
CN 1-Piperazineethanol, 4-[3-(2-chloro-10H-phenothiazin-10-yl)propyl]- (9CI)

(CA INDEX NAME)



RN 100-33-4 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,5-pentanediylbis(oxy)]bis- (9CI) (CA INDEX NAME)



L181 ANSWER 7 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:335212 HCAPLUS
DOCUMENT NUMBER: 132:339369
TITLE: An inhalation system containing a lipid mixture
INVENTOR(S): Pilkiewicz, Frank G.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000027359	A1	20000518	WO 1999-US26858	19991112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2351063	AA	20000518	CA 1999-2351063	19991112
EP 1128813	A1	20010905	EP 1999-958945	19991112

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

JP 2002529393	T2	20020910	JP 2000-580590	19991112
NZ 511568	A	20030829	NZ 1999-511568	19991112
AU 766703	B2	20031023	AU 2000-16212	19991112
ZA 2001003645	A	20020805	ZA 2001-3645	20010504
PRIORITY APPLN. INFO.:			US 1998-108067P	P 19981112
			US 1998-108126P	P 19981112
			WO 1999-US26858	W 19991112

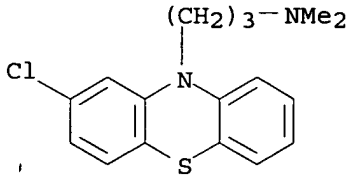
AB A system for administering a bioactive agent by inhalation comprises a lipid mixture containing a phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, sterol, albumin and phosphatidic acid in various combinations and ratios. The biol. active agent is a drug, such as **antitumor** or antimicrobial agent, a compound affecting endocrine function, an antibody, a gene, a cytokine, a differentiating agent, etc.

ED Entered STN: 19 May 2000

IT **50-53-3**, Chlorpromazine, biological studies **58-38-8**, Prochlorperazine **100-33-4**, Pentamidine
RL: **BAC (Biological activity or effector, except adverse)**; **BSU (Biological study, unclassified)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(inhalation system containing lipid mixture for therapy)

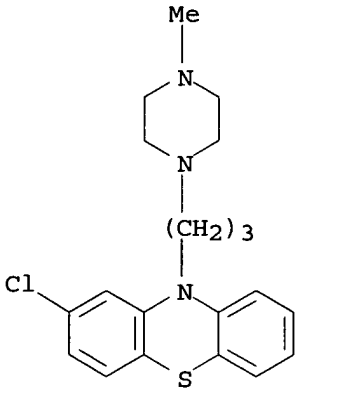
RN 50-53-3 HCAPLUS

CN 10H-Phenothiazine-10-propanamine, 2-chloro-N,N-dimethyl- (9CI) (CA INDEX NAME)



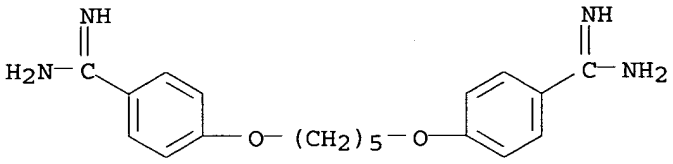
RN 58-38-8 HCAPLUS

CN 10H-Phenothiazine, 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]- (9CI) (CA INDEX NAME)



RN 100-33-4 HCAPLUS

CN Benzenecarboximidamide, 4,4'-[1,5-pentanediylbis(oxy)]bis- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L181 ANSWER 8 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:744969 HCAPLUS
DOCUMENT NUMBER: 130:20593
TITLE: The use of biologically active substances for influencing the extracellular space of sensory cells
INVENTOR(S): Eckmiller, Marion Sangster
PATENT ASSIGNEE(S): Germany
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9850065	A2	19981112	WO 1998-EP1951	19980402
WO 9850065	A3	19990610		
W: AM, AT, AU, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GM, GW, HU, IL, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TT, UA, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
DE 19718826	A1	19981112	DE 1997-19718826	19970505
CA 2288631	AA	19981112	CA 1998-2288631	19980402
AU 9876417	A1	19981127	AU 1998-76417	19980402
EP 980256	A2	20000223	EP 1998-924097	19980402
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: DE 1997-19718826 A 19970505
WO 1998-EP1951 W 19980402

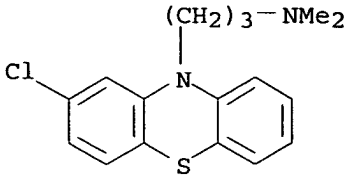
AB The invention relates to the use of an active substance influencing the calcium homeostasis of cells to treat degeneration of sensory cells and adjacent cells. The effect of higher Ca concns. with and without calpain inhibitors on the structure of retinal outer segments was determined

ED Entered STN: 24 Nov 1998

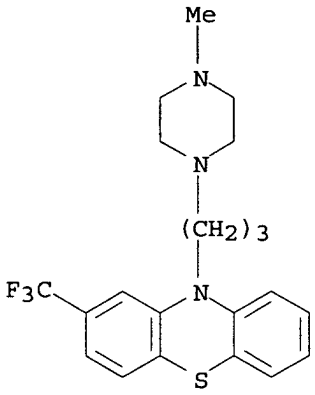
IT **50-53-3**, Chlorpromazine, biological studies **117-89-5**, Trifluoperazine **140-64-7**, Pentamidine isethionate **605-75-4**, Trifluoperazine dimaleate **83016-35-7**
RL: **BAC (Biological activity or effector, except adverse)**; **BSU (Biological study, unclassified)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(drugs for influencing extracellular area of sensory cells)

RN 50-53-3 HCAPLUS

CN 10H-Phenothiazine-10-propanamine, 2-chloro-N,N-dimethyl- (9CI) (CA INDEX NAME)



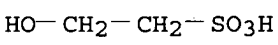
RN 117-89-5 HCAPLUS
CN 10H-Phenothiazine, 10-[3-(4-methyl-1-piperazinyl)propyl]-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



RN 140-64-7 HCAPLUS
CN Ethanesulfonic acid, 2-hydroxy-, compd. with 4,4'-[1,5-pentanediylbis(oxy)]bis[benzenecarboximidamide] (2:1) (9CI) (CA INDEX NAME)

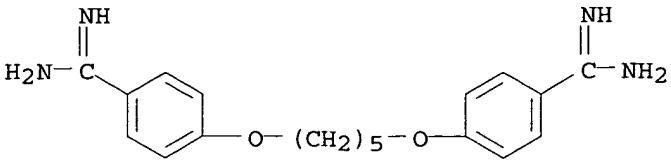
CM 1

CRN 107-36-8
CMF C2 H6 O4 S



CM 2

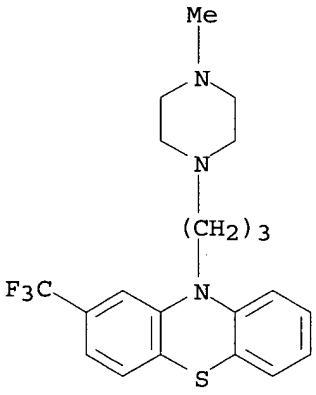
CRN 100-33-4
CMF C19 H24 N4 O2



RN 605-75-4 HCAPLUS
CN 10H-Phenothiazine, 10-[3-(4-methyl-1-piperazinyl)propyl]-2-(trifluoromethyl)-, (2Z)-2-butenedioate (1:2) (9CI) (CA INDEX NAME)

CM 1

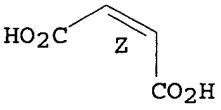
CRN 117-89-5
CMF C21 H24 F3 N3 S



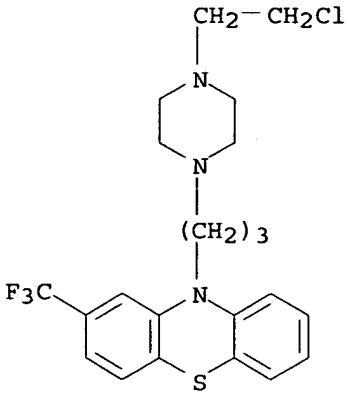
CM 2

CRN 110-16-7
CMF C4 H4 O4

Double bond geometry as shown.



RN 83016-35-7 HCAPLUS
CN 10H-Phenothiazine, 10-[3-[4-(2-chloroethyl)-1-piperazinyl]propyl]-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



L181 ANSWER 9 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:503333 HCAPLUS
DOCUMENT NUMBER: 119:103333
TITLE: Enhanced skin penetration system for improved topical delivery of drugs
INVENTOR(S): Deckner, George Endel; Lombardo, Brian Scott
PATENT ASSIGNEE(S): Richardson-Vicks, Inc., USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9307903	A1	19930429	WO 1992-US8744		19921013
W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG					
AU 9228639	A1	19930521	AU 1992-28639		19921013
AU 675212	B2	19970130			
EP 608322	A1	19940803	EP 1992-921769		19921013
EP 608322	B1	19980722			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE					
JP 07500594	T2	19950119	JP 1993-507771		19921013
JP 3471354	B2	20031202			
HU 67046	A2	19950130	HU 1994-1106		19921013
BR 9206631	A	19951024	BR 1992-6631		19921013
AT 168563	E	19980815	AT 1992-921769		19921013
ES 2118834	T3	19981001	ES 1992-921769		19921013
CA 2117265	C	20000801	CA 1992-2117265		19921013
CN 1072602	A	19930602	CN 1992-113328		19921016
CN 1050763	B	20000329			
US 6277892	B1	20010821	US 1994-191734		19940204
NO 9401317	A	19940616	NO 1994-1317		19940413
FI 9401770	A	19940415	FI 1994-1770		19940415
HK 1013002	A1	20000623	HK 1998-114300		19981221
PRIORITY APPLN. INFO.:			US 1991-778422	A	19911016
			US 1992-948391	A	19920925
			WO 1992-US8744	A	19921013

US 1993-59001 B1 19930506

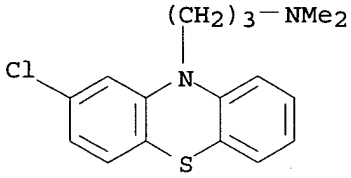
AB A topical composition with enhanced penetration through skin comprises an active agent and a high-mol.-weight crosslinked cationic polymer, such as dialkylaminoalkyl (meth)acrylate polymers. An anti-acne composition contained Alc. SDA-40 40.0, Polyquaternium-32 and mineral oil 4.0, salicylic acid 2.0, and purified water 54.0%.

ED Entered STN: 04 Sep 1993

IT **69-09-0**, Chlorpromazine hydrochloride **16639-82-0**, Chlorpromazine maleate
RL: **BIOL (Biological study)**
(antiemetic compns. containing dialkylaminoalkyl acrylate polymers and)

RN 69-09-0 HCAPLUS

CN 10H-Phenothiazine-10-propanamine, 2-chloro-N,N-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

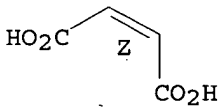
RN 16639-82-0 HCAPLUS

CN 10H-Phenothiazine-10-propanamine, 2-chloro-N,N-dimethyl-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

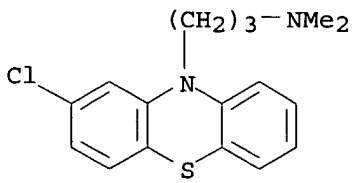
CRN 110-16-7
CMF C4 H4 O4

Double bond geometry as shown.

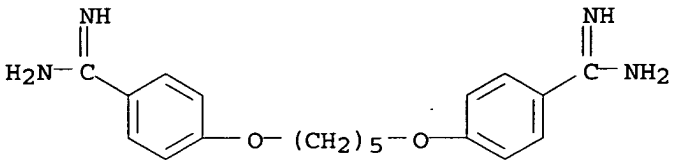


CM 2

CRN 50-53-3
CMF C17 H19 Cl N2 S



IT **100-33-4**, Pentamidine
RL: **BIOL (Biological study)**
(antimicrobial topical compns. containing dialkylaminoalkyl acrylate polymers and)
RN 100-33-4 HCAPLUS
CN Benzenecarboximidamide, 4,4'-[1,5-pentanediylbis(oxy)]bis- (9CI) (CA INDEX NAME)



L181 ANSWER 10 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:503334 HCAPLUS
DOCUMENT NUMBER: 119:103334
TITLE: Enhanced skin penetration system for improved topical delivery of drugs
INVENTOR(S): Deckner, George Endel; Lombardo, Brian Scott
PATENT ASSIGNEE(S): Richardson-Vicks, Inc., USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9307902	A1	19930429	WO 1992-US8741	19921013
W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
AU 9228064	A1	19930521	AU 1992-28064	19921013
AU 675211	B2	19970130		
EP 608320	A1	19940803	EP 1992-921755	19921013
EP 608320	B1	19980128		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE				
HU 74560	A2	19970128	HU 1994-1107	19921013
AT 162725	E	19980215	AT 1992-921755	19921013
ES 2114569	T3	19980601	ES 1992-921755	19921013
CN 1072863	A	19930609	CN 1992-112390	19921016
IN 178157	A	19970308	IN 1992-DE1011	19921105
IN 181010	A	19980411	IN 1992-DE1013	19921105
NO 9401319	A	19940616	NO 1994-1319	19940413
FI 9401771	A	19940415	FI 1994-1771	19940415
US 5756118	A	19980526	US 1995-462258	19950605
US 5756119	A	19980526	US 1995-462376	19950605
US 5773023	A	19980630	US 1995-462710	19950605
US 5780049	A	19980714	US 1995-464991	19950605
US 5776485	A	19980707	US 1995-469701	19950606
US 5874095	A	19990223	US 1998-49367	19980327
PRIORITY APPLN. INFO.:			US 1991-778424 A	19911016

US	1992-957752	B1 19921002
WO	1992-US8741	A 19921013
US	1993-111032	B1 19930824
US	1994-228167	B1 19940415
US	1995-390902	B3 19950216
US	1995-462710	B3 19950605

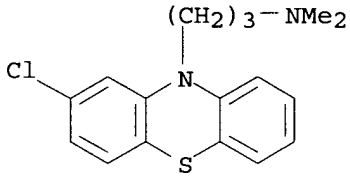
AB A topical composition with enhanced penetration through skin comprises an active agent and a nonionic polyacrylamide having a mol. weight of 1χ106-3χ107. An analgesic composition contained Alc. SDA-40 40.0, ibuprofen 2.0, polyacrylamide/C13-14 isoparaffin/Laureth-7 3.0, and purified water 55.0%.

ED Entered STN: 04 Sep 1993

IT **69-09-0**, Chlorpromazine hydrochloride **16639-82-0**, Chlorpromazine maleate
RL: **BIOL (Biological study)**
(antiemetic compns. containing polyacrylamide and)

RN 69-09-0 HCAPLUS

CN 10H-Phenothiazine-10-propanamine, 2-chloro-N,N-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

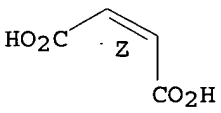
RN 16639-82-0 HCAPLUS

CN 10H-Phenothiazine-10-propanamine, 2-chloro-N,N-dimethyl-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

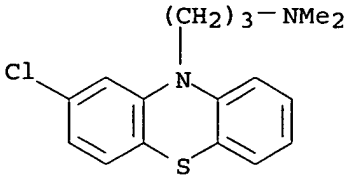
CRN 110-16-7
CMF C4 H4 O4

Double bond geometry as shown.

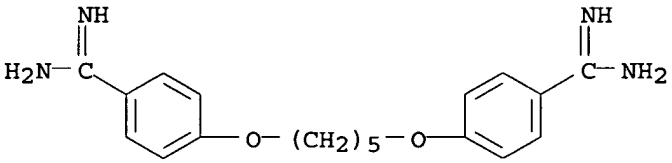


CM 2

CRN 50-53-3
CMF C17 H19 Cl N2 S



IT **100-33-4**, Pentamidine
RL: **BIOL (Biological study)**
(antimicrobial topical compns. containing polyacrylamide and)
RN 100-33-4 HCAPLUS
CN Benzenecarboxamidamide, 4,4'-[1,5-pentanediylbis(oxy)]bis- (9CI) (CA INDEX NAME)



L181 ANSWER 11 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:12199 HCAPLUS
DOCUMENT NUMBER: 114:12199
TITLE: Loading and controlled-release of amphipathic pharmaceuticals to and from liposomes
INVENTOR(S): Barenholz, Yechezkel; Haran, Gilad
PATENT ASSIGNEE(S): Yissum Research Development Co., Israel
SOURCE: Eur. Pat. Appl., 23 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 361894	A2	19900404	EP 1989-309836	19890927
EP 361894	A3	19911121		
EP 361894	B1	19941109		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
IL 91664	A1	19930513	IL 1989-91664	19890918
CA 1335565	A1	19950516	CA 1989-611964	19890919
US 5192549	A	19930309	US 1989-413037	19890927
ES 2067551	T3	19950401	ES 1989-309836	19890927
JP 02196713	A2	19900803	JP 1989-253682	19890928
US 5316771	A	19940531	US 1992-992997	19921218
PRIORITY APPLN. INFO.:			US 1988-250687 A	19880929
			US 1989-413037 A1	19890927

AB A transmembrane loading procedure is given, for efficient loading of amphipathic drugs into liposomes, using the transmembrane gradient of ammonium and pH. The resulting liposomes loaded with the drug are stable and safe. The procedure is equally applicable for sustained-release of liposome-encapsulated drugs. The liposomes may be used in ultrasound imaging to release CO2 to the tissue to enhance hyperchogenicity of

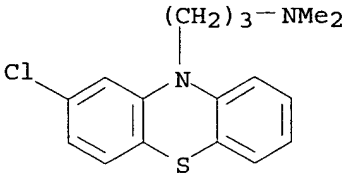
ultrasound imaging. A solution of 100 mg dipalmitoyl phosphatidylcholine and 25 mg cholesterol in 5 mL CHCl3 was subjected to solvent evaporation The thin lipid film obtained was dispersed in 5 mL 0.11 M (NH4)2SO4 containing 0.5 mM desferal and processed into liposomes as usual. Dilution of the liposomes 1,000 times in 0.15 M NaCl containing 0.5 mM desferal created a 1 to 1,000 outside-to-inside (NH4)2SO4 gradient. The liposome dispersion was gel-filtered on Sephadex G-50 and loaded with doxorubicin-HCl.

ED Entered STN: 12 Jan 1991

IT **50-53-3**, Chlorpromazine, biological studies **58-39-9**, Perphenazine **100-33-4**, Pentamidine
RL: **BIOL (Biological study)**
(liposomes containing, transmembrane ammonium or pH gradient for loading and control-release of)

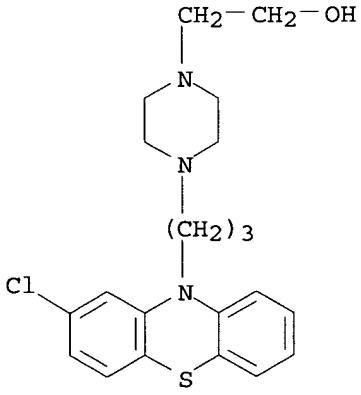
RN 50-53-3 HCAPLUS

CN 10H-Phenothiazine-10-propanamine, 2-chloro-N,N-dimethyl- (9CI) (CA INDEX NAME)



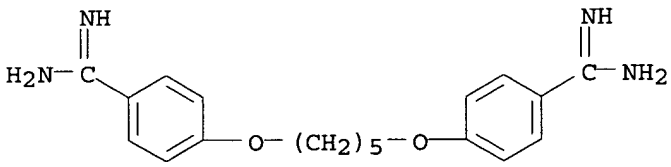
RN 58-39-9 HCAPLUS

CN 1-Piperazineethanol, 4-[3-(2-chloro-10H-phenothiazin-10-yl)propyl]- (9CI) (CA INDEX NAME)



RN 100-33-4 HCAPLUS

CN Benzenecarboximidamide, 4,4'-[1,5-pentanediylbis(oxy)]bis- (9CI) (CA INDEX NAME)



=> d ibib abs hitind 12-34 l181
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, DRUGU, WPIX' -
CONTINUE? (Y)/N:y

L181 ANSWER 12 OF 40 MEDLINE on STN
ACCESSION NUMBER: 97061306 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8905336
TITLE: Effects of calmodulin antagonists and anesthetics on the skin lesions induced by 2-chloroethylethyl sulfide.
AUTHOR: Kim Y B; Hur G H; Choi D S; Shin S; Han B G; Lee Y S; Sok D E
CORPORATE SOURCE: Biomedical Assessment Laboratory (1-4-4), Agency for Defense Development, Taejon, South Korea.
SOURCE: European journal of pharmacology, (1996 Oct 10) 313 (1-2) 107-14.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970306
Last Updated on STN: 19990129
Entered Medline: 19970227

AB The effects of calmodulin antagonists and anesthetics on the skin lesions induced by an alkylating vesicant, 2-chloroethylethyl sulfide, were investigated using female hairless mice. 2-Chloroethylethyl sulfide, topically applied (0.6 microliter/5 mm in diameter) on the back skin of hairless mice, induced mild to moderate petechiae on the 1st day, and ulcers with a thick scab after 3 days. The healing process started after 6 days, resulting in shedding of scabs on 9.52 days. Water-soluble ointment bases showed some beneficial effects, whereas oily bases made the skin lesions worse. Trifluoperazine (0.5-1%) and thioridazine (2%), potent calmodulin antagonists, in Pluronic F-127 base substantially prevented the development of 2-chloroethylethyl sulfide-induced skin lesions. A similar effect was achieved with pentamidine (10%), another type of calmodulin antagonist, but not with ketoconazole, a weak calmodulin antagonist. In addition, anesthetics, such as lidocaine and pentobarbital, showed some protection, although at high concentrations (> 5%). As judged by the microscopic appearance, trifluoperazine successfully reduced the hemorrhage and the infiltration of inflammatory cells in early skin lesions, and the formation of thick scabs, which leads to granulomatous scar tissue in late lesions. These results suggest that some calmodulin antagonists and anesthetics in water-soluble bases might be a choice for the treatment of 2-chloroethylethyl sulfide-induced skin burns.

CT Check Tags: Female
Adjuvants, Anesthesia: PD, pharmacology
Administration, Topical
Anesthetics, Local: PD, pharmacology
Animals
*Burns, Chemical: DT, drug therapy
Burns, Chemical: PA, pathology
*Calmodulin: AI, antagonists & inhibitors
*Dopamine Antagonists: PD, pharmacology
Dosage Forms

Lidocaine: PD, pharmacology
Mice
Mice, Inbred HRS
Mustard Gas: AA, analogs & derivatives
Pentamidine: PD, pharmacology
Pentobarbital: PD, pharmacology
Skin: ME, metabolism
*Thioridazine: PD, pharmacology
*Trifluoperazine: PD, pharmacology

RN **100-33-4 (Pentamidine)**; **117-89-5 (Trifluoperazine)**; 137-58-6 (Lidocaine); **50-52-2 (Thioridazine)**; 505-60-2 (Mustard Gas); 76-74-4 (Pentobarbital)

CN 0 (Adjuvants, Anesthesia); 0 (Anesthetics, Local); 0 (Calmodulin); 0 (Dopamine Antagonists); 0 (Dosage Forms)

L181 ANSWER 13 OF 40 MEDLINE on STN
ACCESSION NUMBER: 95347437 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7542607
TITLE: Inhibition of constitutive nitric oxide synthase in the brain by pentamidine, a calmodulin antagonist.
AUTHOR: Kitamura Y; Arima T; Imaizumi R; Sato T; Nomura Y
CORPORATE SOURCE: Department of Pharmacology, Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan.
SOURCE: European journal of pharmacology, (1995 Apr 28) 289 (2) 299-304.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950911
Last Updated on STN: 19960129
Entered Medline: 19950830

AB Nitric oxide (NO) which is produced by activation of Ca2+/calmodulin-dependent NO synthase is known to induce neuronal damage. We examined the effects of 3'-azido-2',3'-dideoxythymidine (AZT, a reverse transcriptase inhibitor), pentamidine (a therapeutic drug for Pneumocystis carinii pneumonia) and calmodulin antagonists such as trifluoperazine and N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide (W-7) on NO synthase activation. Although AZT had no effect on the activity of constitutive neuronal NO synthase, pentamidine inhibited the activation of neuronal NO synthase as did trifluoperazine and W-7. The inhibition by pentamidine was prevented by the addition of purified calmodulin. In addition, pentamidine inhibited calmodulin-dependent activation of neuronal NO synthase purified from rat cerebellum. From these results, it is suggested that pentamidine inhibits the neuronal NO synthase activation by probably acting as a calmodulin antagonist.

CT Check Tags: Support, Non-U.S. Gov't
*Amino Acid Oxidoreductases: AI, antagonists & inhibitors
Amino Acid Oxidoreductases: DE, drug effects
Animals
Antibodies
*Brain: DE, drug effects
Brain: EN, enzymology
Calmodulin: PD, pharmacology
Cerebellum: DE, drug effects
Dose-Response Relationship, Drug
Immunoblotting
Nitric-Oxide Synthase

*Pentamidine: PD, pharmacology
Rats
Rats, Wistar
Trifluoperazine: PD, pharmacology
Zidovudine: PD, pharmacology
RN **100-33-4 (Pentamidine); 117-89-5 (Trifluoperazine);** 30516-87-1 (Zidovudine)
CN 0 (Antibodies); 0 (Calmodulin); EC 1.14.13.39 (Nitric-Oxide Synthase); EC 1.4. (Amino Acid Oxidoreductases)

L181 ANSWER 14 OF 40 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 1986:265483 BIOSIS
DOCUMENT NUMBER: PREV198631010403; BR31:10403
TITLE: IN-VITRO SCREENS IN THE EXPERIMENTAL **CHEMOTHERAPY** OF LEISHMANIASIS AND TRYPANOSOMIASIS.
AUTHOR(S): CROFT S L [Reprint author]
CORPORATE SOURCE: DEP BIOCHEM PARASITOL, WELLCOME RES LAB, BECKENHAM, KENT BR3 3BS, ENGL, UK
SOURCE: Parasitology Today, (1986) Vol. 2, No. 3, pp. 64-69. CODEN: PATOE2. ISSN: 0169-4758.
DOCUMENT TYPE: Article
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 28 Jun 1986
Last Updated on STN: 28 Jun 1986
CC Cytology - Animal 02506
Cytology - Human 02508
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Carbohydrates 10068
Biochemistry studies - Minerals 10069
Pathology - Therapy 12512
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Clinical pharmacology 22005
Tissue culture, apparatus, methods and media 32500
Chemotherapy - Antiparasitic agents 38510
Parasitology - General 60502
Parasitology - Medical 60504
Invertebrata: comparative, experimental morphology, physiology and pathology - Protozoa 64002
IT Major Concepts
Cell Biology; Parasitology; Pharmacology; Physiology
IT Miscellaneous Descriptors
REVIEW HUMAN MOUSE HAMSTER SODIUM STIBOGLUCONATE PENTAMIDINE ALLOPURINOL FORMYCIN B SINEFUNGIN CHLORPROMAZINE NIFURTIMOX BENZNIDAZOLE RIBOSIDE KETOCONAZOLE BETA LAPACHONE MELARSOPROL SURAMIN DAUNORUBICIN CISPLATIN PHARMACODYNAMICS
ORGN Classifier
Flagellata 35200
Super Taxa
Protozoa; Invertebrata; Animalia
Taxa Notes
Animals, Invertebrates, Microorganisms, Protozoans
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Cricetidae 86310
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 16037-91-5 (SODIUM STIBOGLUCONATE)
100-33-4 (PENTAMIDINE)
315-30-0 (ALLOPURINOL)
13877-76-4 (FORMYCIN B)
58944-73-3 (SINEFUNGIN)
50-53-3 (CHLORPROMAZINE)
23256-30-6 (NIFURTIMOX)
22994-85-0 (BENZNIDAZOLE)
65277-42-1 (KETOCONAZOLE)
4707-32-8 (BETA-LAPACHONE)
494-79-1 (MELARSOPROL)
145-63-1 (SURAMIN)
20830-81-3 (DAUNORUBICIN)
15663-27-1 (CISPLATIN)

L181 ANSWER 15 OF 40 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 1980:17993 BIOSIS
DOCUMENT NUMBER: PREV198018017993; BR18:17993
TITLE: **PROLIFERATIVE** CHANGES IN HUMAN FIBROBLAST CULTURES UNDER THE INFLUENCE OF A SERIES OF DRUGS.
AUTHOR(S): OSTROVSKAYA A A [Reprint author]; LIL'IN E T; GRINBERG K N; STEFANOV S B
CORPORATE SOURCE: SCI-RES INST BIOL TEST CHEM COMPD, MOSCOW, USSR
SOURCE: Pharmaceutical Chemistry Journal (English Translation of Khimiko-Farmatsevticheskii Zhurnal), (1978) Vol. 12, No. 11 PART 1, pp. 1411-1413.
CODEN: PCJOAU. ISSN: 0091-150X.
DOCUMENT TYPE: Article
FILE SEGMENT: BR
LANGUAGE: ENGLISH
CC Cytology - Human 02508
Comparative biochemistry 10010
Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biophysics - Molecular properties and macromolecules 10506
Metabolism - General metabolism and metabolic pathways 13002
Bones, joints, fasciae, connective and adipose tissue - Physiology and biochemistry 18004
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Clinical pharmacology 22005
Toxicology - Pharmacology 22504
Development and Embryology - General and descriptive 25502
Tissue culture, apparatus, methods and media 32500
Plant physiology - Chemical constituents 51522
Pharmacognosy and pharmaceutical botany 54000

IT Major Concepts
Cell Biology; Development; Metabolism; Methods and Techniques; Pharmacology; Skeletal System (Movement and Support); Toxicology
IT Miscellaneous Descriptors
HUMAN FETUS 6 MERCAPTO PURINE DIOXIDINE ISONIAZID ROCCAL SULFALENE APRESSEN SYDNOCARB HALOPERIDOL CHLORPROMAZINE SUXAMETHONIUM HEXAMIDINE NIKETHAMIDE PAPAVERINE DIBASOLE ETHOXYLOTRAN METABOLIC-DRUG
ORGN Classifier
Papaveraceae 26515
Super Taxa
Dicotyledones; Angiospermae; Spermatophyta; Plantae
Taxa Notes
Angiosperms, Dicots, Plants, Spermatophytes, Vascular Plants
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 50-44-2 (6 MERCAPTOPURINE)
17311-31-8 (DIOXIDINE)
54-85-3 (ISONIAZID)
152-47-6 (SULFALENE)
34262-84-5 (SYDNOCARB)
52-86-8 (HALOPERIDOL)
50-53-3 (CHLORPROMAZINE)
306-40-1 (SUXAMETHONIUM)
125-33-7Q (HEXAMIDINE)
3811-75-4Q (HEXAMIDINE)
59-26-7 (NIKETHAMIDE)
58-74-2 (PAPAVERINE)

L181 ANSWER 16 OF 40 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 2
ACCESSION NUMBER: 95343350 EMBASE
DOCUMENT NUMBER: 1995343350
TITLE: Compatibility and activity of aldesleukin (recombinant interleukin-2) in presence of selected drugs during simulated Y-site administration: Evaluation of three methods.
AUTHOR: Alex S.; Gupta S.L.; Minor J.R.; Turcovski-Corrales S.; Gallelli J.F.; Taub D.; Piscitelli S.C.
CORPORATE SOURCE: Pharmacy Department, Warren G. Magnuson Clinical Center, National Institutes of Health,Bethesda, MD 20892, United States
SOURCE: American Journal of Health-System Pharmacy, (1995) 52/21 (2423-2426).
ISSN: 1079-2082 CODEN: AHSPEK
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The compatibility and biological activity of aldesleukin (a form of recombinant interleukin-2) in the presence of selected i.v. drugs during simulated Y-site administration was studied. Five milliliters of aldesleukin 33,800 IU/mL in 5% dextrose injection was mixed in glass test

tubes with 5 mL of each of 19 i.v. drugs prepared at concentrations used in routine clinical practice. The compatibility of the combinations was assessed by visual examination and spectrophotometry at 0, 0.5, 1, and 2 hours after preparation, and bioassays were conducted to determine the activity of aldesleukin in the combinations. Lorazepam was the only drug visually incompatible with aldesleukin. All the secondary drugs were spectrophotometrically compatible with aldesleukin. However, the bioassays showed that the following drugs reduced the activity of aldesleukin: ganciclovir sodium, lorazepam, pentamidine isethionate, prochlorperazine edisylate, and promethazine hydrochloride. Thus, aldesleukin became less biologically active when combined with four drugs for which visual examination suggested compatibility and when combined with five drugs for which spectrophotometry indicated compatibility. Aldesleukin 33,800 IU/mL in 5% dextrose injection lost significant biological activity in the presence of prochlorperazine edisylate, promethazine hydrochloride, lorazepam, ganciclovir sodium, and pentamidine isethionate during simulated Y-site administration. Visual assessment and spectrophotometry may not be valid methods for assessing possible changes in the biological activity of aldesleukin when combined with other agents.

CT Medical Descriptors:
*drug mixture
*immune deficiency: DT, drug therapy
article
combination chemotherapy
drug activity
human
hypotension: SI, side effect
influenza: SI, side effect
priority journal
simulation
spectrophotometry
Drug Descriptors:
***lorazepam: IT, drug interaction**
***recombinant interleukin 2: CB, drug combination**
*recombinant interleukin 2: DO, drug dose
*recombinant interleukin 2: PR, pharmaceutics
***recombinant interleukin 2: IT, drug interaction**
*recombinant interleukin 2: DT, drug therapy
*recombinant interleukin 2: PD, pharmacology
*recombinant interleukin 2: AE, adverse drug reaction
*recombinant interleukin 2: AD, drug administration
anticoagulant agent: DT, drug therapy
anticoagulant agent: IT, drug interaction
anticoagulant agent: CB, drug combination
antiemetic agent: DT, drug therapy
antiemetic agent: CB, drug combination
antiemetic agent: IT, drug interaction
antiinfective agent: DT, drug therapy
antiinfective agent: IT, drug interaction
antiinfective agent: CB, drug combination
cotrimoxazole: CB, drug combination
cotrimoxazole: IT, drug interaction
cotrimoxazole: DT, drug therapy
diphenhydramine: CB, drug combination
diphenhydramine: IT, drug interaction
diphenhydramine: DT, drug therapy
dopamine: DT, drug therapy
dopamine: IT, drug interaction
dopamine: CB, drug combination
electrolyte: DT, drug therapy

electrolyte: IT, drug interaction
electrolyte: CB, drug combination
foscarnet: DT, drug therapy
foscarnet: IT, drug interaction
foscarnet: CB, drug combination
ganciclovir: CB, drug combination
ganciclovir: IT, drug interaction
ganciclovir: DT, drug therapy
gluconate calcium: DT, drug therapy
gluconate calcium: CB, drug combination
gluconate calcium: IT, drug interaction
glucose: CB, drug combination
heparin: IT, drug interaction
heparin: DT, drug therapy
heparin: CB, drug combination
histamine h2 receptor antagonist: IT, drug interaction
histamine h2 receptor antagonist: DT, drug therapy
histamine h2 receptor antagonist: CB, drug combination
isethionic acid: CB, drug combination
isethionic acid: IT, drug interaction
isethionic acid: DT, drug therapy
magnesium sulfate: CB, drug combination
magnesium sulfate: IT, drug interaction
magnesium sulfate: DT, drug therapy
metoclopramide: DT, drug therapy
metoclopramide: IT, drug interaction
metoclopramide: CB, drug combination
ondansetron: DT, drug therapy
ondansetron: CB, drug combination
ondansetron: IT, drug interaction
pentamidine: IT, drug interaction
pentamidine: DT, drug therapy
pentamidine: CB, drug combination
potassium chloride: CB, drug combination
potassium chloride: IT, drug interaction
potassium chloride: DT, drug therapy
prochlorperazine: IT, drug interaction
prochlorperazine: CB, drug combination
prochlorperazine: DT, drug therapy
promethazine: DT, drug therapy
promethazine: IT, drug interaction
promethazine: CB, drug combination
ranitidine: IT, drug interaction
ranitidine: DT, drug therapy
ranitidine: CB, drug combination
thiethylperazine: DT, drug therapy
thiethylperazine: IT, drug interaction
thiethylperazine: CB, drug combination

RN (lorazepam) 846-49-1; (recombinant interleukin 2) 110942-02-4; (cotrimoxazole) 8064-90-2; (diphenhydramine) 147-24-0, 58-73-1; (dopamine) 51-61-6, 62-31-7; (foscarnet) 4428-95-9; (ganciclovir) 82410-32-0; (gluconate calcium) 299-28-5; (glucose) 50-99-7, 84778-64-3; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (isethionic acid) 107-36-8; (magnesium sulfate) 7487-88-9; (metoclopramide) 12707-59-4, 2576-84-3, 364-62-5, 7232-21-5; (ondansetron) 103639-04-9, 116002-70-1, 99614-01-4; (pentamidine) **100-33-4**; (potassium chloride) 7447-40-7; (prochlorperazine) **58-38-8**; (promethazine) 58-33-3, 60-87-7; (ranitidine) 66357-35-5, 66357-59-3; (thiethylperazine) **1420-55-9**

CN (1) Proleukin

CO (1) Chiron (United States); Du pont; Smith kline beecham; Elkins sinn;

Sandoz; Glaxo; Wyeth; Lyphomed; Schein; Abbott; Roerig; Astra; Syntex; Fujisawa; Burroughs wellcome; Baxter; Hoffmann la roche (United States); Squibb

L181 ANSWER 17 OF 40 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004364621 EMBASE

TITLE: [Recent advances on leishmaniasis **chemotherapy**: Intracelular molecules as a drug target]. RECENTES AVANCOS DA QUIMIOTERAPIA DAS LEISHMANIOSES: MOLECULAS INTRACELULARES COMO ALVO DE FARMACOS.

AUTHOR: Soares-Bezerra R.J.; Leon L.; Genestra M.

CORPORATE SOURCE: M. Genestra, Departamento de Imunologia, Lab. Bioquim. Tripanossomatideos, Instituto Oswaldo Cruz - FIOCRUZ/RJ, Av. Brasil, 4365 - Manguinhos, 21045-900 - Rio de Janeiro, Brazil. genestra@ioc.fiocruz.br

SOURCE: Revista Brasileira de Ciencias Farmaceuticas/Brazilian Journal of Pharmaceutical Sciences, (2004) 40/2 (139-149). Refs: 84
ISSN: 1516-9332 CODEN: RBCFFM

COUNTRY: Brazil

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 004 Microbiology
013 Dermatology and Venereology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: Portuguese

SUMMARY LANGUAGE: English; Portuguese

AB The leishmaniases are diseases caused by protozoan parasites Leishmania sp., that are present in promastigotes or amastigotes forms; the promastigotes infect the sand fly vector, and the amastigotes are the infective forms presented on human macrophages. These protozooses showed two types of clinical manifestations: tegumentar and visceral. The clinical treatments used have shown inefficient; the drugs utilized are presented in injectable form, difficulting the treatment, since to be the patient, may be interned for applications, which are painful. Therefore, for internation, it is necessary monitoring the collateral effects of the drugs, as these medications showed a high toxicity. The leishmaniasis **chemotherapy** is the target of studies of many research laboratories, that have tested other compounds and plant extracts with the aim of finding new leishmanicidal agents with lower colateral effects and good bioavailability. Therefore, the researches aimed to find other pharmaceutical forms, that do not lead to patient internation. This paper aims to review the recent advances of the **chemotherapy** used for leishmaniasis, presenting the pharmacological and biochemical aspects of the participation of intracellular molecules of parasite as the drug targets.

CT Medical Descriptors:
*leishmaniasis: DT, drug therapy
*leishmaniasis: ET, etiology
Leishmania
fly
amastigote
promastigote
skin leishmaniasis: DT, drug therapy
skin leishmaniasis: ET, etiology
visceral leishmaniasis: DT, drug therapy
visceral leishmaniasis: ET, etiology
drug efficacy
gastrointestinal symptom: SI, side effect

myalgia: SI, side effect
heart arrhythmia: SI, side effect
pancreatitis: SI, side effect
nausea: SI, side effect
headache: SI, side effect
hypotension: SI, side effect
tachycardia: SI, side effect
hyperglycemia: SI, side effect
fever: SI, side effect
hypertension: SI, side effect
kidney dysfunction: SI, side effect
drug effect
vomiting: SI, side effect
diarrhea: SI, side effect
human
nonhuman
review
Drug Descriptors:
*plant extract
*antileishmanial agent: AE, adverse drug reaction
***antileishmanial agent: CB, drug combination**
*antileishmanial agent: DO, drug dose
*antileishmanial agent: DT, drug therapy
*antileishmanial agent: IM, intramuscular drug administration
*antileishmanial agent: IV, intravenous drug administration
*folic acid antagonist
*DNA topoisomerase inhibitor: DT, drug therapy
*antimony derivative: AE, adverse drug reaction
***antimony derivative: CB, drug combination**
*antimony derivative: DO, drug dose
*antimony derivative: DT, drug therapy
*antimony derivative: IM, intramuscular drug administration
*antimony derivative: IV, intravenous drug administration
*amidine: AE, adverse drug reaction
*amidine: DO, drug dose
*amidine: DT, drug therapy
*amidine: IV, intravenous drug administration
trifluralin: DT, drug therapy
ketoconazole: DT, drug therapy
itraconazole: DT, drug therapy
mevinolin: DT, drug therapy
terbinafine: DT, drug therapy
9 anilinoacridine derivative: DT, drug therapy
mepacrine: DT, drug therapy
chlorpromazine: DT, drug therapy
organometallic compound: DT, drug therapy
stibogluconate sodium: CB, drug combination
stibogluconate sodium: DT, drug therapy
meglumine antimonate: DT, drug therapy
diminazene aceturate: DO, drug dose
diminazene aceturate: DT, drug therapy
benzamidine derivative: DT, drug therapy
local anesthetic agent
n,n' diphenylbenzamidine
methoxyamidine
pentamidine: AE, adverse drug reaction
pentamidine: DO, drug dose
pentamidine: DT, drug therapy
pentamidine: IV, intravenous drug administration
diphenylbenzamidine

antibiotic agent: AE, adverse drug reaction
antibiotic agent: CB, drug combination
antibiotic agent: DT, drug therapy
amphotericin B: AE, adverse drug reaction
amphotericin B: DT, drug therapy
amphotericin B lipid complex: DT, drug therapy
amphotericin B cholesterol sulfate: DT, drug therapy
paromomycin: CB, drug combination
paromomycin: DO, drug dose
paromomycin: DT, drug therapy
unindexed drug: CB, drug combination
unindexed drug: DO, drug dose
unindexed drug: DT, drug therapy
unclassified drug
pentostan

RN (trifluralin) 1582-09-8; (ketoconazole) 65277-42-1; (itraconazole) 84625-61-6; (mevinolin) 75330-75-5; (terbinafine) 91161-71-6; (mepacrine) 69-05-6, 83-89-6; (chlorpromazine) **50-53-3**, **69-09-0**; (stibogluconate sodium) 16037-91-5; (meglumine antimonate) 133-51-7; (diminazene aceturate) 908-54-3; (pentamidine) **100-33-4**; (amphotericin B) 1397-89-3, 30652-87-0; (amphotericin B cholesterol sulfate) 120895-52-5; (paromomycin) 11035-13-5, 1263-89-4, 1390-73-4, 51795-47-2, 54597-56-7, 7542-37-2, 84420-34-8

CN (1) Ambisome; (2) Amphotec; (3) Abelcet; Glucantime; Berenil; Pentostan

CO (1) Fujisawa (United States); (2) Sequs (United States); (3) Liposome Company (United States)

L181 ANSWER 18 OF 40 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003255116 EMBASE
TITLE: Systematic discovery of multicomponent therapeutics.
AUTHOR: Borisy A.A.; Elliott P.J.; Hurst N.W.; Lee M.S.; Lehar J.; Price E.R.; Serbedzija G.; Zimmermann G.R.; Foley M.A.; Stockwellt B.R.; Keith C.T.
CORPORATE SOURCE: B.R. Stockwellt, Whitehead Inst. for Biomed. Research, Nine Cambridge Center, Cambridge, MA 02142, United States. stockwell@wi.mit.edu
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (24 Jun 2003) 100/13 (7977-7982). Refs: 46
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Multicomponent therapies, originating through deliberate mixing of drugs in a clinical setting, through happenstance, and through rational design, have a successful history in a number of areas of medicine, including **cancer**, infectious diseases, and CNS disorders. We have developed a high-throughput screening method for identifying effective combinations of therapeutic compounds. We report here that systematic screening of combinations of small molecules reveals unexpected interactions between compounds, presumably due to interactions between the pathways on which they act. Through systematic screening of ≈120,000 different two-component combinations of reference-listed drugs, we identified potential multicomponent therapeutics, including (i) fungistatic and analgesic agents that together generate fungicidal activity in drug-resistant Candida albicans, yet do not significantly affect human

cells, (ii) glucocorticoid and antiplatelet agents that together suppress the production of **tumor** necrosis factor-α in human primary peripheral blood mononuclear cells, and (iii) antipsychotic and antiprotozoal agents that do not exhibit significant **antitumor** activity alone, yet together prevent the growth of **tumors** in mice. Systematic combination screening may ultimately be useful for exploring the connectivity of biological pathways and, when performed with reference-listed drugs, may result in the discovery of new combination drug regimens.

CT Medical Descriptors:
*drug mixture
*drug screening
methodology
Candida albicans
colony forming unit
cytokine production
cancer: DT, drug therapy
human
nonhuman
mouse
animal experiment
animal model
human cell
article
priority journal
Drug Descriptors:
***antifungal agent: CB, drug combination**
*antifungal agent: PR, pharmaceutics
***analgesic agent: CB, drug combination**
*analgesic agent: PR, pharmaceutics
***fungicide: CB, drug combination**
*fungicide: PR, pharmaceutics
***glucocorticoid: CB, drug combination**
*glucocorticoid: PR, pharmaceutics
***antithrombocytic agent: CB, drug combination**
*antithrombocytic agent: PR, pharmaceutics
***neuroleptic agent: CB, drug combination**
*neuroleptic agent: PR, pharmaceutics
tumor necrosis factor alpha: EC, endogenous compound
antiprotozoal agent: PR, pharmaceutics
fluconazole: PR, pharmaceutics
phenazopyridine: PR, pharmaceutics
gamma interferon: EC, endogenous compound
chlorpromazine: CB, drug combination
chlorpromazine: DT, drug therapy
chlorpromazine: PR, pharmaceutics
pentamidine: CB, drug combination
pentamidine: DT, drug therapy
pentamidine: PR, pharmaceutics
paclitaxel: CB, drug combination
paclitaxel: DT, drug therapy
amphotericin: CB, drug combination
amphotericin: PR, pharmaceutics
ciclopirox: CB, drug combination
ciclopirox: PR, pharmaceutics
clotrimazole: CB, drug combination
clotrimazole: PR, pharmaceutics
econazole: CB, drug combination
econazole: PR, pharmaceutics
haloprogin: CB, drug combination

haloprogin: PR, pharmaceutics
ketoconazole: CB, drug combination
ketoconazole: PR, pharmaceutics
metronidazole: CB, drug combination
metronidazole: PR, pharmaceutics
miconazole: CB, drug combination
miconazole: PR, pharmaceutics
sulconazole: CB, drug combination
sulconazole: PR, pharmaceutics
cladribine: CB, drug combination
cladribine: PR, pharmaceutics
cupric chloride: CB, drug combination
cupric chloride: PR, pharmaceutics
dacarbazine: CB, drug combination
dacarbazine: PR, pharmaceutics
disulfiram: CB, drug combination
disulfiram: PR, pharmaceutics
estradiol: CB, drug combination
estradiol: PR, pharmaceutics
verapamil: CB, drug combination
verapamil: PR, pharmaceutics
unindexed drug

RN (fluconazole) 86386-73-4; (phenazopyridine) 136-40-3, 94-78-0; (gamma interferon) 82115-62-6; (chlorpromazine) **50-53-3**, **69-09-0**; (pentamidine) **100-33-4**; (paclitaxel) 33069-62-4; (amphotericin) 12633-72-6; (ciclopirox) 29342-05-0; (clotrimazole) 23593-75-1; (econazole) 24169-02-6, 27220-47-9; (haloprogin) 777-11-7; (ketoconazole) 65277-42-1; (metronidazole) 39322-38-8, 443-48-1; (miconazole) 22916-47-8; (sulconazole) 61318-90-9, 61318-91-0; (cladribine) 4291-63-8; (cupric chloride) 7447-39-4; (dacarbazine) 4342-03-4; (disulfiram) 97-77-8; (estradiol) 50-28-2; (verapamil) 152-11-4, 52-53-9

CO Inter Chem Laboratories (United States); Sigma

L181 ANSWER 19 OF 40 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003475683 EMBASE
TITLE: Successful Treatment of Balamuthia Amoebic Encephalitis: Presentation of 2 Cases.
AUTHOR: Deetz T.R.; Sawyer M.H.; Billman G.; Schuster F.L.; Visvesvara G.S.
CORPORATE SOURCE: Dr. F.L. Schuster, California Dept. of Health Services, Viral and Rickettsial Dis. Lab., 850 Marina Bay Pkwy., Richmond, CA 94804, United States. fschuste@dhs.ca.gov
SOURCE: Clinical Infectious Diseases, (15 Nov 2003) 37/10 (1304-1312).
Refs: 34
ISSN: 1058-4838 CODEN: CIDIEL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Case histories are presented of 2 individuals (a 5-year-old girl and 64-year-old man) who developed encephalitis caused by the free-living amoeba Balamuthia mandrillaris. Both individuals survived after diagnosis

and initiation of effective antimicrobial therapy. Immunostaining for Balamuthia-specific antibody levels identified the causative agent of the infections. Antimicrobial therapy with flucytosine, pentamidine, fluconazole, sulfadiazine, and a macrolide antibiotic (azithromycin or clarithromycin) was initiated. Phenothiazines (thioridazine and trifluoperazine) were also used. Both patients recovered, and there was no evidence of recrudescence of the disease at 2 and 6 years after onset of symptoms. Awareness of Balamuthia as the causative agent of encephalitis and early initiation of antimicrobial therapy were critical to the recovery of both patients. Although optimal antimicrobial therapy for Balamuthia amoebic encephalitis has yet to be determined, the antimicrobials used in these 2 cases effectively controlled the disease. These 2 individuals are the only known survivors of this otherwise fatal type of amoebic encephalitis.

CT Medical Descriptors:
*encephalitis: DI, diagnosis
*encephalitis: DT, drug therapy
*encephalitis: ET, etiology
*Balamuthia mandrillaris
***sarcomastigophora infection: DI, diagnosis**
***sarcomastigophora infection: DT, drug therapy**
***sarcomastigophora infection: ET, etiology**
antimicrobial activity
immunohistochemistry
virus identification
clinical feature
emergency ward
computer assisted tomography
nuclear magnetic resonance imaging
biopsy
anamnesis
family history
tuberculin test
laboratory test
hospital admission
brain biopsy
clinical examination
hospital discharge
brain vasculitis: DI, diagnosis
fungal cell culture
acid fast bacterium
lumbar puncture
skin biopsy
treatment withdrawal
muscle rigidity: SI, side effect
disease course
artificial ventilation
myoclonus
coma
kidney failure
liver toxicity: SI, side effect
pancreatitis
hyperglycemia: DT, drug therapy
hyperglycemia: SI, side effect
intensive care unit
rehabilitation center
functional assessment
blood sampling
blood cell count
Herpes simplex virus

virus encephalitis: DT, drug therapy
interstitial nephritis: SI, side effect
glucose blood level
human
male
female
case report
preschool child
adult
article
priority journal
Drug Descriptors:
*antiinfective agent: AE, adverse drug reaction
***antiinfective agent: CB, drug combination**
*antiinfective agent: DT, drug therapy
*antiinfective agent: IV, intravenous drug administration
*antiinfective agent: PO, oral drug administration
flucytosine: CB, drug combination
flucytosine: DT, drug therapy
flucytosine: PO, oral drug administration
pentamidine: AE, adverse drug reaction
pentamidine: CB, drug combination
pentamidine: DT, drug therapy
pentamidine isethionate: CB, drug combination
pentamidine isethionate: DT, drug therapy
pentamidine isethionate: IV, intravenous drug administration
fluconazole: AE, adverse drug reaction
fluconazole: CB, drug combination
fluconazole: DT, drug therapy
sulfadiazine: CB, drug combination
sulfadiazine: DT, drug therapy
sulfadiazine: PO, oral drug administration
macrolide: CB, drug combination
macrolide: DT, drug therapy
azithromycin: AE, adverse drug reaction
azithromycin: CB, drug combination
azithromycin: DT, drug therapy
clarithromycin: CB, drug combination
clarithromycin: DT, drug therapy
phenothiazine derivative: CB, drug combination
phenothiazine derivative: DT, drug therapy
thioridazine: CB, drug combination
thioridazine: DT, drug therapy
trifluoperazine: AE, adverse drug reaction
trifluoperazine: CB, drug combination
trifluoperazine: DT, drug therapy
dexamethasone: DT, drug therapy
prednisone: DT, drug therapy
tuberculostatic agent: CB, drug combination
tuberculostatic agent: DT, drug therapy
amphotericin B: CB, drug combination
amphotericin B: DT, drug therapy
doxycycline: CB, drug combination
doxycycline: DT, drug therapy
ceftriaxone: CB, drug combination
ceftriaxone: DT, drug therapy
aciclovir: DT, drug therapy
ketoconazole: CB, drug combination
ketoconazole: DT, drug therapy
metronidazole: DT, drug therapy

recombinant human insulin: DT, drug therapy
isoniazid: CB, drug combination
isoniazid: DT, drug therapy
rifampicin: CB, drug combination
rifampicin: DT, drug therapy
ethambutol: CB, drug combination
ethambutol: DT, drug therapy
pyrazinamide: CB, drug combination
pyrazinamide: DT, drug therapy
liver enzyme: EC, endogenous compound
glucose: EC, endogenous compound
RN (flucytosine) 2022-85-7; (pentamidine) **100-33-4**; (pentamidine isethionate) **140-64-7**; (fluconazole) 86386-73-4; (sulfadiazine) 547-32-0, 68-35-9; (azithromycin) 83905-01-5; (clarithromycin) 81103-11-9; (thioridazine) **130-61-0**, **50-52-2**; (trifluoperazine) **117-89-5**, **440-17-5**; (dexamethasone) 50-02-2; (prednisone) 53-03-2; (amphotericin B) 1397-89-3, 30652-87-0; (doxycycline) 10592-13-9, 17086-28-1, 564-25-0; (ceftriaxone) 73384-59-5, 74578-69-1; (aciclovir) 59277-89-3; (ketoconazole) 65277-42-1; (metronidazole) 39322-38-8, 443-48-1; (isoniazid) 54-85-3, 62229-51-0, 65979-32-0; (rifampicin) 13292-46-1; (ethambutol) 10054-05-4, 1070-11-7, 3577-94-4, 74-55-5; (pyrazinamide) 98-96-4; (glucose) 50-99-7, 84778-64-3

L181 ANSWER 20 OF 40 EMBASE
on STN
ACCESSION NUMBER: 2003448118 EMBASE
TITLE: Combine and conquer.
AUTHOR: Farley S.
SOURCE: Nature Reviews Drug Discovery, (2003) 2/8 (606).
Refs: 1
ISSN: 1474-1776 CODEN: NRDDAG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 004 Microbiology
016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
CT Medical Descriptors:
*drug screening
drug potentiation
drug efficacy
drug design
drug activity
drug determination
antifungal activity
Candida albicans
cancer inhibition
human
note
priority journal
Drug Descriptors:
antifungal agent: DV, drug development
antifungal agent: PD, pharmacology
tumor necrosis factor alpha
fluconazole
neuroleptic agent: CB, drug combination
neuroleptic agent: CM, drug comparison
neuroleptic agent: PD, pharmacology
chlorpromazine: CB, drug combination

chlorpromazine: CM, drug comparison
chlorpromazine: PD, pharmacology
antiprotozoal agent: CB, drug combination
antiprotozoal agent: CM, drug comparison
antiprotozoal agent: PD, pharmacology
pentamidine: CB, drug combination
pentamidine: CM, drug comparison
pentamidine: PD, pharmacology
antineoplastic agent: CM, drug comparison
antineoplastic agent: PD, pharmacology
paclitaxel: CM, drug comparison
paclitaxel: PD, pharmacology
RN (fluconazole) 86386-73-4; (chlorpromazine) **50-53-3**, **69-09-0**; (pentamidine) **100-33-4**; (paclitaxel) 33069-62-4

L181 ANSWER 21 OF 40 EMBASE
on STN
ACCESSION NUMBER: 2003371512 EMBASE
TITLE: Leishmaniasis: Efflux pumps and chemoresistance.
AUTHOR: Leandro C.; Campino L.
CORPORATE SOURCE: C. Leandro, Unidade de Micobacterias, Inst. de Higiene e Medicina Tropical, Universidade Nova de Lisboa, Rua Junqueira 96, Lisboa 1349-008, Portugal. cleandro@ihmt.unl.pt
SOURCE: International Journal of Antimicrobial Agents, (1 Sep 2003) 22/3 (352-357).
Refs: 80
ISSN: 0924-8579 CODEN: IAAGEA
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Resistance of parasitic protozoa such as Leishmania to therapeutic drugs continues to escalate in developing countries. Treatment programs for human leishmaniasis are still based on pentavalent antimonials but resistance to these compounds has been a persistent problem. In many instances, resistance of the parasite is due to over-expressed ABC efflux pumps. In Leishmania different classes of ABC transporters extrude antimonials, azoles and folates resulting in drug-resistant phenotypes. Although some studies have focused on developing inhibitors against these resistant phenotypes, new efficient modulators that are able to inhibit drug efflux are needed. .COPYRGT. 2003 Elsevier B.V. and the International Society of **Chemotherapy.** All rights reserved.
CT Medical Descriptors:
*visceral leishmaniasis: DT, drug therapy
*skin leishmaniasis: DT, drug therapy
antibiotic resistance
drug transport
drug efficacy
treatment outcome
treatment failure
drug mechanism
drug effect
sequence homology
gene amplification
human
nonhuman

clinical trial
review
priority journal
Drug Descriptors:
antimony derivative: CB, drug combination
antimony derivative: DT, drug therapy
pyrrole derivative: DT, drug therapy
pyrrole derivative: PD, pharmacology
folic acid derivative: DT, drug therapy
stibogluconate sodium: DT, drug therapy
meglumine antimonate: DT, drug therapy
pentamidine: DT, drug therapy
paromomycin: DT, drug therapy
paromomycin: PD, pharmacology
amphotericin B: CB, drug combination
amphotericin B: DT, drug therapy
amphotericin B: PD, pharmacology
miltefosine: DT, drug therapy
miltefosine: PO, oral drug administration
itraconazole: CT, clinical trial
itraconazole: DT, drug therapy
allopurinol: CT, clinical trial
allopurinol: CB, drug combination
allopurinol: DT, drug therapy
allopurinol: PD, pharmacology
aminoglycoside antibiotic agent: DT, drug therapy
aminoglycoside antibiotic agent: PA, parenteral drug administration
allylamine
terbinafine
ketoconazole: CB, drug combination
ketoconazole: DT, drug therapy
fluconazole: DT, drug therapy
edelfosine: DT, drug therapy
ABC transporter
multidrug resistance protein
vinblastine
daunorubicin
puromycin
doxorubicin
verapamil
quinidine
cyclosporin A
methotrexate
arsenic trioxide
thioridazine
unindexed drug
pentostan

RN (stibogluconate sodium) 16037-91-5; (meglumine antimonate) 133-51-7; (pentamidine) **100-33-4**; (paromomycin) 11035-13-5, 1263-89-4, 1390-73-4, 51795-47-2, 54597-56-7, 7542-37-2, 84420-34-8; (amphotericin B) 1397-89-3, 30652-87-0; (miltefosine) 58066-85-6; (itraconazole) 84625-61-6; (allopurinol) 315-30-0; (allylamine) 107-11-9; (terbinafine) 91161-71-6; (ketoconazole) 65277-42-1; (fluconazole) 86386-73-4; (edelfosine) 65492-82-2; (multidrug resistance protein) 149200-37-3, 208997-77-7; (vinblastine) 865-21-4; (daunorubicin) 12707-28-7, 20830-81-3, 23541-50-6; (puromycin) 53-79-2, 58-58-2; (doxorubicin) 23214-92-8, 25316-40-9; (verapamil) 152-11-4, 52-53-9; (quinidine) 56-54-2; (cyclosporin A) 59865-13-3, 63798-73-2; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (arsenic trioxide) 1303-24-8, 1327-53-3, 13464-58-9, 15502-74-6; (thioridazine) **130-61-0**, **50-52-2**

CN Pentostan; Glucantime

L181 ANSWER 22 OF 40 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003072492 EMBASE
TITLE: [Role of linezolid in antimicrobial therapy].
PAPEL DE LINEZOLID EN TERAPEUTICA ANTIMICROBIANA.
AUTHOR: Carmona P.-M.; Roma E.; Monte E.; Garcia J.; Gobernado M.
CORPORATE SOURCE: Dr. P.-M. Carmona, Servicio de Farmacia, Hospital la Fe, Avda. Campanar, 21, 46009 Valencia, Spain. pcarmonag@sefh.es
SOURCE: Enfermedades Infecciosas y Microbiologia Clinica, (2003) 21/1 (30-41).
Refs: 75
ISSN: 0213-005X CODEN: EIMCE2
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: Spanish
SUMMARY LANGUAGE: English; Spanish

AB The progressive emergence of multi-resistant gram-positive strains has prompted the search for new molecules (quinolones, streptogramins, oxazolidinones, ketolides, glycopeptides, daptomycin) to add to the current therapeutic arsenal. Linezolid, the first commercially available member of the oxazolidinone family, has evidenced activity against multi-resistant gram-positive strains (methicillin-resistant Staphylococcus aureus, S. aureus with decreased glycopeptide sensitivity, vancomycin-resistant Enterococcus spp., Streptococcus pneumoniae with decreased sensitivity to penicillin and cephalosporins), thereby providing a new option for treating infections by these microorganisms. This work reviews the microbiologic and pharmacologic aspects of this agent in order to establish its position among the available options for antimicrobial **chemotherapy.**

CT Medical Descriptors:
*antimicrobial therapy
multidrug resistance
Gram positive bacterium
antibiotic resistance
drug activity
Staphylococcus infection: DR, drug resistance
Staphylococcus infection: DT, drug therapy
methicillin resistant Staphylococcus aureus
antibiotic sensitivity
Streptococcus pneumonia: DR, drug resistance
Streptococcus pneumonia: DT, drug therapy
Enterococcus
Streptococcus pneumoniae
penicillin resistance
antimicrobial activity
drug structure
drug mechanism
drug effect
diarrhea: SI, side effect
nausea: SI, side effect
vomiting: SI, side effect
side effect: SI, side effect
pseudomembranous colitis: SI, side effect

thrush: SI, side effect
vagina candidiasis: SI, side effect
hypertension: SI, side effect
dyspepsia: SI, side effect
abdominal pain: SI, side effect
pruritus: SI, side effect
insomnia: SI, side effect
liver toxicity: SI, side effect
heart atrium fibrillation: SI, side effect
kidney failure: SI, side effect
pancreatitis: SI, side effect
bone marrow suppression: SI, side effect
drug efficacy
human
nonhuman
review
Drug Descriptors:
*linezolid: AE, adverse drug reaction
*linezolid: CM, drug comparison
*linezolid: DO, drug dose
***linezolid: IT, drug interaction**
*linezolid: DT, drug therapy
*linezolid: PK, pharmacokinetics
*linezolid: PD, pharmacology
*linezolid: IV, intravenous drug administration
*linezolid: PO, oral drug administration
quinoline derived antiinfective agent
streptogramin
oxazolidinone derivative
ketolide
glycopeptide
daptomycin
penicillin derivative
vancomycin: CM, drug comparison
meticillin
cephalosporin derivative
amphotericin B: IT, drug interaction
chlorpromazine: IT, drug interaction
diazepam: IT, drug interaction
pentamidine: IT, drug interaction
erythromycin: IT, drug interaction
phenytoin: IT, drug interaction
cotrimoxazole: IT, drug interaction
ceftriaxone: CM, drug comparison
cefpodoxime: CM, drug comparison
oxacillin: CM, drug comparison
dicloxacillin: CM, drug comparison
RN (linezolid) 165800-03-3; (daptomycin) 103060-53-3; (vancomycin) 1404-90-6, 1404-93-9; (meticillin) 132-92-3, 38882-79-0, 61-32-5; (amphotericin B) 1397-89-3, 30652-87-0; (chlorpromazine) **50-53-3**, **69-09-0** ; (diazepam) 439-14-5; (pentamidine) **100-33-4**; (erythromycin) 114-07-8, 70536-18-4; (phenytoin) 57-41-0, 630-93-3; (cotrimoxazole) 8064-90-2; (ceftriaxone) 73384-59-5, 74578-69-1; (cefpodoxime) 82619-04-3; (oxacillin) 1173-88-2, 66-79-5, 7240-38-2; (dicloxacillin) 13412-64-1, 3116-76-5, 343-55-5

L181 ANSWER 23 OF 40 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002297862 EMBASE
TITLE: Promising therapeutic targets for antileishmanial drugs.

AUTHOR: Werbovetz K.A.
CORPORATE SOURCE: K.A. Werbovetz, Div. of Med. Chemistry/Pharmacognosy, College of Pharmacy, The Ohio State University, 500 West 12th Avenue, Columbus, OH 43210, United States. werbovetz.1@osu.edu
SOURCE: Expert Opinion on Therapeutic Targets, (2002) 6/4 (407-422).
Refs: 131
ISSN: 1472-8222 CODEN: EOTTAO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Current treatments for the parasitic disease leishmaniasis are unsatisfactory due to their route of administration, toxicity and expense. Resistance is also developing to first-line antimonial drugs. Fortunately, a handful of antileishmanial agents, such as the orally available compound miltefosine, are currently in clinical trials. In addition, several promising drug targets and lead molecules are being studied with the goal of developing new antileishmanial agents. Drug candidates have been identified through the continued investigation of parasite sterol metabolism and parasite proteases. New antileishmanial molecules have also been discovered through the study of novel targets and pathways, such as the bisphosphonate inhibitors of isoprenoid biosynthesis. This review presents a synopsis of the drug targets and lead compounds that have been investigated over the last few years against leishmaniasis, gives a perspective on the **chemotherapeutic** potential of each and discusses some of the obstacles of antileishmanial drug development.
CT Medical Descriptors:
*leishmaniasis: DT, drug therapy
drug targeting
treatment failure
drug toxicity
drug cost
drug bioavailability
clinical study
drug identification
sterol metabolism
biosynthesis
drug effect
drug efficacy
drug potentiation
drug structure
drug screening
drug synthesis
human
nonhuman
mouse
animal experiment
animal model
controlled study
human cell
animal tissue
animal cell
review
Drug Descriptors:
*antileishmanial agent: DV, drug development

antimony derivative: DT, drug therapy
miltefosine: DT, drug therapy
miltefosine: PK, pharmacokinetics
miltefosine: PD, pharmacology
miltefosine: PO, oral drug administration
proteinase
bisphosphonic acid derivative: DV, drug development
isoprenoid
proteinase inhibitor: DV, drug development
amphotericin B: AN, drug analysis
amphotericin B: CB, drug combination
amphotericin B: CM, drug comparison
amphotericin B: DT, drug therapy
amphotericin B: PD, pharmacology
amphotericin B: IP, intraperitoneal drug administration
itraconazole: CB, drug combination
itraconazole: DT, drug therapy
itraconazole: PD, pharmacology
posaconazole: AN, drug analysis
posaconazole: CB, drug combination
posaconazole: CM, drug comparison
posaconazole: DT, drug therapy
posaconazole: PD, pharmacology
posaconazole: PO, oral drug administration
terbinafine: CB, drug combination
terbinafine: DT, drug therapy
terbinafine: PD, pharmacology
manumycin: DV, drug development
manumycin: PD, pharmacology
risedronic acid: DV, drug development
risedronic acid: DT, drug therapy
risedronic acid: PD, pharmacology
risedronic acid: IP, intraperitoneal drug administration
phenothiazine derivative: CM, drug comparison
phenothiazine derivative: PD, pharmacology
chlorpromazine: CB, drug combination
chlorpromazine: PD, pharmacology
theophylline derivative: DV, drug development
theophylline derivative: PD, pharmacology
1,4 naphthoquinone derivative: DV, drug development
1,4 naphthoquinone derivative: PD, pharmacology
menadione: AN, drug analysis
menadione: DV, drug development
menadione: PD, pharmacology
plumbagin: AN, drug analysis
plumbagin: DV, drug development
plumbagin: PD, pharmacology
quinazoline derivative: AN, drug analysis
quinazoline derivative: DV, drug development
quinazoline derivative: PD, pharmacology
glutathione derivative: DV, drug development
glutathione derivative: PD, pharmacology
eflornithine: DT, drug therapy
eflornithine: PD, pharmacology
n(g) hydroxyarginine: DV, drug development
n(g) hydroxyarginine: PD, pharmacology
cotrimoxazole: DT, drug therapy
cotrimoxazole: PD, pharmacology
2,4 diamino 5 benzylpyrimidine derivative: DV, drug development
2,4 diamino 5 benzylpyrimidine derivative: PD, pharmacology

cystatin: AN, drug analysis
cystatin: CB, drug combination
cystatin: DV, drug development
cystatin: IT, drug interaction
cystatin: PD, pharmacology
alpha interferon: CB, drug combination
alpha interferon: DV, drug development
alpha interferon: IT, drug interaction
alpha interferon: PD, pharmacology
trifluralin: DV, drug development
trifluralin: PD, pharmacology
pentamidine: DT, drug therapy
pentamidine: PD, pharmacology
pentamidine: PA, parenteral drug administration
unindexed drug

RN (miltefosine) 58066-85-6; (proteinase) 9001-92-7; (proteinase inhibitor) 37205-61-1; (amphotericin B) 1397-89-3, 30652-87-0; (itraconazole) 84625-61-6; (posaconazole) 171228-49-2; (terbinafine) 91161-71-6; (manumycin) 52665-74-4; (risedronic acid) 105462-24-6, 122458-82-6; (chlorpromazine) **50-53-3**, **69-09-0**; (theophylline derivative) 2850-40-0; (menadione) 58-27-5; (plumbagin) 481-42-5; (eflornithine) 67037-37-0, 70052-12-9; (cotrimoxazole) 8064-90-2; (cystatin) 81989-95-9; (trifluralin) 1582-09-8; (pentamidine) **100-33-4**

CN (1) Bactrim; (2) Actonel; (3) Lamisil; (4) Posaconazole; (5) Sporanox; Thorazine

CO (1) Bioscience; (2) Aventis; (3) Novartis; (4) Schering Plough; (5) Pfizer

L181 ANSWER 24 OF 40 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-06003 DRUGU P S
TITLE: Mississippi mud in the 1990s. Risks and outcomes of vancomycin-associated toxicity in general oncology practice.
AUTHOR: Elting L S; Rubenstein E B; Kurtin D; Rolston K V I; Fangtang J; Martin C G; Raad I I; Whimbey E E; Manzullo E; Bodey G P
CORPORATE SOURCE: Univ.Texas
LOCATION: Houston, Tex., USA
SOURCE: Cancer (83, No. 12, 2597-607, 1998) 1 Fig. 9 Tab. 37 Ref.
CODEN: CANCAR ISSN: 0008-543X
AVAIL. OF DOC.: Department of Internal Medicine Specialities, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Box 40, Houston, TX 77030, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1999-06003 DRUGU P S
AB A study of toxicity associated with p.o. vancomycin (VA) in 742 consecutive **cancer** patients led to the development of a clinical prediction rule, the Nephrotoxicity Risk Score (NRS). Other side-effects included phlebitis (associated with central venous catheters, (CVC), rashes (in patients on beta-lactam antibiotics (BL) and ototoxicity, mostly with concomitant ototoxic agents, such as aminoglycosides (AM) and cisplatin (CI). The risk of nephrotoxicity was increased by coadministration of amphotericin B (AB), AM, foscarnet, cyclosporin (CS), polymixin B, pentamidine and combinations of carboplatin, NSAID and CY but was not reliably predicted by an increased Cmax of VA.
ABEX Methods The records of 742 **cancer** patients (average age 51 yr, 50% male, 47% hematologic, 12% genitourinary, 10% breast **tumors**), who received more than 1 course of VA, were reviewed

during therapy. Results 97 Patients (13%) had had BMT, 83% had CVC and about 50% were neutropenic. VA (2 g/day in 72% patients) was prescribed for infection in 84% patients, 29% with gram positive bacteremia and administered prophylactically in 120 patients (16%, commonly 1 g/day) for an average 16 days. 647 Patients (87%) received a BL, 87 (12%) AM (amikacin) and 15% AB. Cmax for VA was determined in 61% patients. Phlebitis occurred in 21 (3%) patients, 'red person syndrome' in 10 patients, skin rashes in 82 patients (11%, 78% administered BL) and ototoxocity in 18/319 and 12/423 patients with and without other ototoxic agents (high frequency loss in 1 patient given VA without ototoxic agents, 2 with CI or furosemide and trimethoprim plus sulfamethoxazole). Nephrotoxicity developed in 127/726 patients (17%), 26% vs. 16% after VA (1 vs. 2 g/day). 36% Of patients who received AM, AB, CY or CI developed nephrotoxicity, 5 who required dialysis received other toxic agents. NRS, which included scores for concomitant treatment was more sensitive than standard assessment of the risk of nephrotoxicity. (E8/LG)

L181 ANSWER 25 OF 40 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1995-18435 DRUGU M
TITLE: Use of semiquantitative PCR to assess onset and treatment of Pneumocystis carinii infection in rat model.
AUTHOR: O'Leary T J; Tsai M M; Wright C F; Cushion M T
CORPORATE SOURCE: Univ.Cincinnati
LOCATION: Washington, D.C.; Cincinnati, Ohio, USA
SOURCE: J.Clin.Microbiol. (33, No. 3, 718-24, 1995) 5 Fig. 5 Tab. 47 Ref.
CODEN: JCMIDW ISSN: 0095-1137
AVAIL. OF DOC.: Department of Cellular Pathology, Armed Forces Institute of Pathology, Washington, D.C. 20306-6000, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1995-18435 DRUGU M
AB Semiquantitative polymerase chain reaction (SQPCR) and cyst counts were used to assess Pneumocystis carinii pneumoniae infections in bronchoalveolar lavage (BAL) fluids and homogenized lung tissue of rats immunosuppressed (IMS) with methylprednisolone (MP, DepoMedrol, Upjohn) for 3 to 12 wk. Similarly, the effects on infection of tapering rats off steroid treatment or of treating the IMS rats with pentamidine isetionate (PE, **LymphoMed**) or with trimethoprim-sulfamethoxazole (TMP-SMX, Wellcome) were measured. The SQPCR signal rose throughout immunosuppression and fell fastest with PE or TMP-SMX treatment. There was significant correlation between SQPCR results from lung homogenates and BAL fluids and a strong correlation between these SQPCR results and corresponding cyst counts.
ABEX Methods Sasco Sprague-Dawley rats were either immunosuppressed with MP (4 mg/wk) or not for up to 12 wk. Some rats were weaned off MP after 6 wk, MP dose being halved in each of the next 3 wk. SQPCR measurements and cyst counts were done immediately or after a further 3, 5 or 8 wk off MP. Other IMS rats were given TMP-SMX (250 mg/kg/day) for 10, 21 or 42 days or PE (10 mg/kg) for 5, 7 or 18 days, starting after the 1st 6 wk of MP (4 mg/kg). Results There was a large rise in mean square SQPCR signals for lung tissue and BAL fluid from IMS rats between 0 and 3 wk, with a slight rise over the next 9 wk. Results obtained by SQPCR were qualitatively similar, but not identical, to those obtained by cyst counting. SQPCR results for P. carinii pneumonia infection in lung homogenate and BAL fluid in rats weaned off MP approached pre-immunosuppression levels by the end of the study. TMP-SMX caused a rapid fall in the SQPCR assay of IMS rat lung homogenate, results after

10 days of treatment being similar to those from non-IMS control rats. Results from SQPCR assay of BAL fluid from rats treated with TMP-SMX did not fall as rapidly as those from lung homogenate. SQPCR results of lung homogenate and BAL fluid paralleled each other closely after PE treatment but seemed not to be as dramatic as those after TMP-SMX treatment. The correlation between lung homogenate and BAL fluid SQPCR results was significant with a Pearson correlation coefficient of 0.435 but there was substantial scatter. The correlation between cyst counting and SQPCR tested with the Wilcoxon signed rank test was strong. (JE)

L181 ANSWER 26 OF 40 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1994-16767 DRUGU T M S
TITLE: Aerosolized Pentamidine for the Prevention of Pneumocystis carinii Pneumonia in Children With **Cancer** Intolerant or Allergic to Trimethoprim/ Sulfamethoxazole.
AUTHOR: Mustafa M M; Pappo A; Cash J; Winick N J; Buchanan G R
CORPORATE SOURCE: Univ.Texas
LOCATION: Dallas, Texas, United States
SOURCE: J.Clin.Oncol. (12, No. 2, 258-61, 1994) 3 tab. 28 Ref.
CODEN: JCONDN ISSN: 0732-183X
AVAIL. OF DOC.: Department of Pediatrics, University of Texas Southwestern Medical center, 5323 Harry Hines Blvd., Dallas, TX 75235-9063, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1994-16767 DRUGU T M S
AB Aerosolized pentamidine (PT) was effective and generally well-tolerated when given as prophylaxis against Pneumocystis carinii pneumonia (PCP) among 60 children with **cancer** who had had severe adverse reactions to trimethoprim (TP) + sulfamethoxazole (SZ). Patients were suffering from acute lymphoblastic **leukemia** (ALL), acute myelogenous **leukemia** (AML), non-**Hodgkin**'s **lymphoma** (NHL), osteosarcoma, Ewing's **sarcoma** and undifferentiated **sarcoma.** Adverse reactions to aerosolized PT included bronchospasm (in some cases requiring aerosolized salbutamol, Allen+Hanburys), cough, vomiting and nausea. Prior adverse reactions to TP/SZ included myelosuppression, urticaria and angioedema and persistent mucosal ulcerations.
ABEX Methods 60 Children (29 male, aged 3-19, median age 12 yr) with ALL (46/60), AML (5/60), NHL (2/60) or solid **tumors** (7/60, osteosarcoma, Ewing's **sarcoma** and undifferentiated **sarcoma**) received aerosolized PT at 200 mg/sq.m every 4 wk as prophylaxis against PCP. 720 Doses of PT were administered over 21600 patient days, and 30/60 patients were treated for at least 12 mth (range 12-25 mth). All patients had previously experienced severe adverse reactions to TP/SX, including myelosuppression in 50%, allergic reactions, including urticaria and angioedema, in 35% and persistent mucosal ulcerations in 8%. Results No patient developed PCP during the study. 15% Of patients had transient cough lasting from 1-10 min. 6/60 Patients developed 1 or more episodes of bronchospasm that necessitated bronchodilator treatment. In 1 patient, bronchospasm was severe enough to required a switch from aerosolized to i.b. PT. A 2nd patients with severe bronchospasm on PT was switched to TP/SX without undue reaction. 1/60 Patients had nausea, vomiting and cough during the 1st 2 treatments and was switched to i.v. PT. No patient had rash, nephrotoxicity, hematological abnormalities or glucose intolerance on aerosolized PT. 2/60 Patients had abdominal pain and vomiting 7 and 10 days after aerosolized PT; none had evidence of pancreatitis. (E61/MB)

L181 ANSWER 27 OF 40 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1993-35258 DRUGU M T S E
TITLE: Primary Peripheral Nodal **Lymphoma** in Children.
AUTHOR: Wollner N; Exelby P; Lindsley K L; Lieberman P; Filippa D; Heller G
LOCATION: New York, New York, United States
SOURCE: Cancer (71, No. 11, 3670-79, 1993) 1 Fig. 6 Tab. 17 Ref.
CODEN: CANCAR ISSN: 0008-543X
AVAIL. OF DOC.: Pediatric Day Hospital, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1993-35258 DRUGU M T S E
AB The event-free and **lymphoma**-free survival rates (EFSR and LFSR, respectively) were high in a study of 40 pediatric patients with primary peripheral nodal **lymphoma** treated with the LSA2-L2 protocol (prednisone, vincristine, daunorubicin, L-asparaginase, carmustine, tioguanine, cyclophosphamide, hydroxyurea, methotrexate and cytarabine). Toxic effects included anemia, leukopenia, thrombocytopenia, renal failure, convulsions, bacterial and Pneumocystis carinii pneumonia (treated with pentamidine), sepsis due to E. coli, Staph. aureus and albus and Propionibacterium, Herpes Zoster, fever, elevated amylase levels, joint pain and swelling, skin rash, neurosarcoma, neck muscle atrophy, azoospermia, lymphedema, benign thyroid nodule and xerostomia. Radiotherapy and dose intensity of **chemotherapy** promoted rapid and complete cell killing and thus prevented the emergence of resistant cells.
ABEX Methods 40 Patients (26 male, median age 10 yr) with primary peripheral nodal **lymphoma** (stage I-IV) received the LSA2-L2 protocol which included prednisone, vincristine, cyclophosphamide (CY), daunorubicin, L-asparaginase, carmustine, tioguanine, hydroxyurea, methotrexate (MX) and cytarabine (CB). Radiotherapy (30-55 Gy over 3-4 wk or 20 GY over 10-20 days) was administered to patients with lymph nodes larger than 5 cm in diameter, during induction or consolidation. Results Nodal primary sites were above the diaphragm, in the right cervical chain, the left cervical area and the right and left supraclavicular area. Patients had hepatosplenomegaly. 32 (80%) Patients received radiotherapy. Toxic effects of treatment included anemia, leukopenia, thrombocytopenia, renal failure, convulsions, bacterial and Pneumocystis carinii pneumonia (treated with pentamidine), sepsis due to E. coli, Staph. aureus and albus and Propionibacterium, Herpes Zoster, fever, elevated amylase levels, joint pain and swelling, skin rash, neurosarcoma, neck muscle atrophy, azoospermia, lymphedema, benign thyroid nodule and xerostomia. EFSR was 75% and median follow-up was 12.8 yr. **Lymphoma** recurred in 3 patients. SR were 81% and 78.5% in males and females, respectively. 24 10-Yr-old and 16 greater than 10-yr-old patients had SR of 79.2% and 81.2%, respectively. There was no significant difference in survival between the patients with lymphoblastic and histiocytic or high-grade and medium-grade **lymphomas.** LDH in the primary site was not indicative of extent or bulk of disease and did not affect survival negatively. (KP)

L181 ANSWER 28 OF 40 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1993-55120 DRUGU M
TITLE: Experimental Visceral Leishmaniasis: Role of trans-Aconitic Acid in Combined **Chemotherapy.**
AUTHOR: Kar S; Kar K; Bhattacharya P K; Ghosh D K

LOCATION: Calcutta, India
SOURCE: Antimicrob.Agents Chemother. (37, No. 11, 2459-65, 1993) 1 Fig. 4 Tab. 37 Ref.
CODEN: AMACCQ ISSN: 0066-4804
AVAIL. OF DOC.: Leishmania Group, Indian Institute of Chemical Biology, 4, Raja S.C. Mullick Road, Calcutta 700 032, India.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1993-55120 DRUGU M
AB Trans-aconitic acid (TAA) inhibited in-vitro growth of Leishmania donovani promastigotes in a dose-dependent way, which was reversed by addition of cis-aconitic acid (CAA) or citrate (both Sigma-Chemical). The strong inhibitory activity of TAA against transformation and multiplication within peritoneal macrophages of L. donovani amastigotes in-vitro was enhanced by simultaneous addition of Na stibogluconate (SB, Wellcome), pentamidine (PE, May+Baker) or allopurinol (AP, Sigma-Chemical). TAA was effective in-vivo against L. donovani in hamster spleens when given p.o., i.p. or, especially, i.m. In experimental visceral leishmaniasis in hamsters (1 mth or 8 day models), TAA combined with SB, PE or AP was more inhibitory in-vivo than any of the 4 drugs alone.
ABEX Treatment in-vitro of L. donovani amastigotes within BALB/c mouse peritoneal macrophages with TAA (5 mM), TAA (10 mM), SB (20 ug/ml), TAA (5 mM) + SB (20 ug/ml), PE (2 ug/ml), TAA (5 mM) + PE (2 ug/ml), AP (5 ug/ml) or TAA (5 mM) + AP (5 ug/ml) inhibited the number of infected macrophages by 25, 41.7, 15.7, 100, 29.2, 100, 22 and 46%, respectively. TAA (200 mg/kg/day) given p.o., i.p. or i.m. to male Syrian golden hamsters suppressed the spleen parasite burden by 73.2. 71.9 and 77.0%, respectively. TAA (200 or 400 mg/kg/day, p.o. for 5 days), SB (50 mg/kg/day, i.p. on each of 3 alternate days), PE (8 mg/kg/day, i.p. on each of 3 alternate days) and AP (15 mg/kg/day, p.o. for 5 days) suppressed the spleen parasite burden of 8 day infected hamsters in-vivo by 62.5. 98.5, 30 and 7%, respectively. TAA (200 mg/kg/day) + SB, TAA + PE and TAA + AP reduced the spleen parasite burden of 8 day infected hamsters by 87, 90 and 79.2%, respectively; corresponding combination with TAA (400 mg/kg/day) caused 98.8, 99.7 and 99% suppression. In a similar in-vivo 1 mth model, TAA (200 or 400 mg/kg/day), SB (50 or 100 mg/kg/day), AP (15 mg/kg/day) and PE (8 mg/kg/day) reduced the spleen parasite burden by 73.5, 99.8, 35, 72, 22 and 20%, respectively. TAA (200 mg/kg/day) + SB (50 mg/kg/day), TAA (400 mg/kg/day) + SB, SB + AP (15 mg/kg/day), SB (100 mg/kg/day) + AP, TAA (200 mg/kg/day) + AP, TAA (400 mg/kg/day) + AP, TAA (200 mg/kg/day) + PE (8 mg/kg/day) and TAA (400 mg/kg/day) + PE reduced the spleen parasite burden in the 1 mth model by 98, about 100, 45, 89, 97, about 100, 98.9 and about 100%, respectively. (M65/PJ) (D.K.G.).

L181 ANSWER 29 OF 40 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1992-50497 DRUGU T M S
TITLE: High Dose **Chemotherapy** and Autologous Bone Marrow Transplantation in Advanced **Hodgkin**'s Disease.
AUTHOR: Morgan M J; Dodds A J; Wolf M; Januszewicz H; Ma D; Downs K
LOCATION: Sydney, Melbourne, Australia
SOURCE: Med.J.Aust. (157, No. 8, 527-30, 1992) 2 Fig. 3 Tab. 20 Ref.
CODEN: MJAUAJ ISSN: 0025-729X
AVAIL. OF DOC.: Haematology Department, St. Vincent's Hospital, Darlinghurst, NSW 2010, Australia. (A.J.D., 7 authors).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature
AN 1992-50497 DRUGU T M S
AB In a prospective, multicenter open study of 17 patients, autologous bone marrow transplantation after CVB (cyclophosphamide (Cy), etoposide (ET) and carmustine (CM) or Bu-Cy (p.o. busulfan + i.v. Cy), was effective therapy for advanced **Hodgkin**'s disease. Bicarbonate, mesna, antiemetics and s.c. granulocyte colony stimulating factor (G-CSF, Amgen) were also given. Previous drugs used were MOPP (chlormethine, vincristine, procarbazine, prednisone), ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and other **chemotherapy.** Complications were fever, mucositis, hemorrhagic cystitis, bacteria or interstitial pneumonia (which responded to ganciclovir, pentamidine and corticosteroids), veno-occlusive disease (VOD), hypotension, cardiac arrhythmia, sepsis, GI bleeding, pulmonary emboli (PE) and death (in 5 patients).
ABEX Methods 17 Patients (14 male, median age 30 yr, range 19-49) were considered for transplantation after previous treatment: radiotherapy (13 patients); MOPP or equivalent (17); AVBD or equivalent (13); and other **chemotherapy** (5). A median of 29 mth (9-178 mth) after diagnosis of advanced **Hodgkin**'s disease they received an autologous bone marrow transplant preceded by high-dose **chemotherapy** including CVB in 14 patients (Cy, 1.5-1.8 g/sq.m on day -7 to day -4; ET, 0.2-0.6 g/sq.m on day -7 to day -5; and CM, 0.3-0.6 g/sq.m on day -3) and Bu-Cy in 3 patients (Bu, 4 mg/kg/day on day -7 to -4 and Cy, 60 mg/kg/day on day -3 and -2.). Patients were hydrated i.v. while on **chemotherapy** and given bicarbonate during Cy infusion. 2 Patients were given mesna. All received antiemetic therapy and 3 were given G-CSF (20 ug/kg from day 1) which was then reduced and discontinued. Results 10/17 Patients (59%) had CR and 4/17 (24%) had PR. The actuarial survival at 30 mth was 70%. Within a treatment-sensitive group 8/9 (including 5 who had CR before transplantation) patients remained disease-free at a median follow-up (FU) of 2 mth. Disease-free survival at 30 mth was 85%. 2/8 treatment-resistant patients had CR at 20 and 28 mth FU and 3 had PR of which 1 died from pulmonary disease at 8 mth FU and 2 still had PR at 19 and 29 mth FU, respectively. There were 3 PR, 1 of whom died. There were 3 other deaths (2 at 6 and 13 mth and 1 transplant-related, caused by GI bleeding and multiple PE. 30 Mth actuarial disease-free survival was 45%. In patients who did not recieve G-CSF, the median time to recovery of granulocyte levels was 22 days compared with 15 in the 3 patients who did receive G-CSF. (KKP)

L181 ANSWER 30 OF 40 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1992-25129 DRUGU M T S
TITLE: A Comparison of the Effectiveness of Three Regimens in the Prevention of Pneumocystis carinii Pneumonia in Human Immunodeficiency Virus-Infected Patients.
AUTHOR: Martin M A; Cox P H; Beck K; Styer C M; Beall G N
LOCATION: Torrance, California, United States
SOURCE: Arch.Intern.Med. (152, No. 3, 523-28, 1992) 5 Tab. 28 Ref.
CODEN: AIMDAP ISSN: 0003-9926
AVAIL. OF DOC.: No Reprint Address.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1992-25129 DRUGU M T S
AB P.o. trimethoprim with sulfamethoxazole (TS) was more effective than p.o. dapsone (DS) and aerosolized pentamidine (PA) in the prophylaxis of Pneumocystis carinii pneumonia (PCP) in a retrospective chart review of

211 AIDS or AIDS-related complex (ARC) patients. Concurrent antiretroviral treatment included zidovudine or 2+,3+-dideoxyinosine (ddI). Side-effects included cytopenia, erythroderma/fever, liver function abnormality, GI intolerance and G-6-PD abnormality with TS and DS and bronchospasm/cough with PA. Concurrent complications were wasting syndrome, Kaposi's **sarcoma**, esophageal candidiasis, cryptococcal meningitis, Isospora belli infection, extrapulmonary tuberculosis, Toxoplasma gondii infection, HIV dementia and disseminated herpes simplex virus infection; TS prevented I. belli and T. gondii infection.

ABEX Methods 211 Patients (196 male; aged 23-65 yr, mean 36.7) with AIDS (151) or ARC (60) received TS (1 double-strength tablet b.i.d. or t.i.d.) on 3 alternate days/wk for 1-25 (mean 7.4 mth) in 133 patients, 77 received DS (50 mg/day) for 1-23 (mean 5.7 mth) and 125 received PA (300 mg 1 x mth) for 1-21 (mean 9.3 mth). Primary prophylaxis was given to 62% patients, and 73% received antiretroviral treatment including zidovudine (500 mg/day) in 115 patients and ddI in 22. Concurrent conditions were wasting syndrome, Kaposi's **sarcoma**, esophageal, candidiasis, cryptococcal meningitis, Isopora belli infection, extrapulmonary tuberculosis, Toxoplasma gondii infection, HIV dementia and disseminated herpes simplex virus infection. Results 22 Patients (10%) developed PCP; 15 (19%) of secondary prophylaxis and 7 (5%) of primary prophylaxis patients developed the infection. None of the PCP patients received TS and no patient developed T. gondii encephalitis or I. belli diarrhea while receiving TS. 5 Patients contracted PCP while taking DS, 1 developed I. belli and 1 developed cerebral toxoplasmosis. 17 Patients developed PCP while on PA. Change from PA treatment was due to bronchospasm/cough in 2 cases. Change from DS was due to erythroderma/fever in 14 cases, cytopenia in 16 cases, liver function abnormality in 1 case, GI intolerance in 5 cases, G-6-PD abnormality in 3 cases and other reasons in 3 cases; corresponding incidences in these effects for TS were 30, 22, 7, 12 and 0. 56% TS patients, 55% DS patients and 2% PA patients experienced adverse effects. (E4/AE)

L181 ANSWER 31 OF 40 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1993-09992 DRUGU M
TITLE: **Chemotherapy** of CNS-Trypanosomiasis: The Combined Use of Diminazene Aceturate or Pentamidine with DL-alpha-difluoromethylornithine (DFMO).
AUTHOR: Jennings F W
LOCATION: Glasgow, United Kingdom
SOURCE: Trop.Med.Parasitol. (43, No. 2, 106-09, 1992) 3 Tab. 13 Ref.
CODEN: TMPAEY ISSN: 0177-2392
AVAIL. OF DOC.: Department of Veterinary Parasitology, University of Glasgow, Bearsden Road, Glasgow G61 1QH, Scotland.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1993-09992 DRUGU M
AB I.p. diminazene aceturate (DA; Berenil, Hoechst) was more efficient than i.p. pentamidine (PA; Lomidine. Rhone-Merieux) in combination with continuous p.o. DL-alpha-difluoromethylornithine (DFMO; Eflornithine, Merrell-Dow) against experimental Trypanosoma (T.) brucei infection in mice. Addition of melarsenoxyde cysteamine (mel Cy; Cymelarsan) to DFMO did not improve cure rates of DA or PA. It is considered unlikely that DFMO + DA would be a suitable treatment in cases of melarsoprol relapses.
ABEX 21/22 T. brucei-infected CD-1 mice (25-30 g) treated with DFMO (2% for 15 days starting 21 days after infection) + DA (40 mg/kg) after 3 days were permanently cured. In 20 treated with DFMO + DA after 7 days, 20/20

died. When treatment with DFMO was reduced to 6 days DA (40 mg/kg), 5/6 mice were cured. There were no cures with PA 50 mg + DFMO 2% for 15 days, but increasing the PA dose rate to 100 mg/kg resulted in cures (5/6 or 6/6) in 4 different regimen of PA admininstration (100 g on day 24, 2 x 100 g on days 24 and 25, 3 x 100 g on days 24-26 and 4 x 100 g on days 24-27). The addition of PA 4 days after starting DFMO to the combination DFMO for 16 days + mel Cy (2.5 mg/kg) on the last 2 days of treatment either had no effect or even reduced the efficacy of the DFM)/mel Cy. (E4/RB)

L181 ANSWER 32 OF 40 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1992-04903 DRUGU T M S
TITLE: Visceral Leishmaniasis in an HIV-Infected Patient: Clinical Features and Response to Treatment.
AUTHOR: Fenske S; Stellbrink H J; Albrecht H; Greten H
LOCATION: Hamburg, Germany,West
SOURCE: Klin.Wochenschr. (69, No. 17, 793-96, 1991) 1 Fig. 1 Tab. 16 Ref.
CODEN: KLWOAZ
AVAIL. OF DOC.: Medizinische Kernklinik und Poliklinik, Universitaets-Krankenhaus Eppendorf, Martinistrasse 52, W-2000 Hamburg 20, Germany.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1992-04903 DRUGU T M S
AB The case is reported of a 43-yr-old patient with HIV infection who developed visceral leishmaniasis as the 1st infectious complication.Bone marrow showed accumulation of Leishmania donovani. Treatment with i.v. Na stibogluconate (G, Pentostram) was initially successful, but he relapsed after 7 mth and chronic suppressive treatment was continued with i.v. pentamidine isethionate (PM). Legionella pneumophila pneumonia was treated with erythromycin (EM) and ciprofloxacin (CF), and Kaposi's **sarcoma** was treated with alpha-interferon (aIF), zidovudine (ZV) and s.c. gamma IF (gIF). Rifampicin (RF) caused allergic exanthema. Antimony treatment was well tolerated apart from fever, decreased patients and development of Kaposi's **sarcoma**. The patient's physical condition improved markedly and he returned to work on PM.
ABEX A 43-yr-old homosexual patient with HIV infection who travelled frequently to the Far East, developed fever, malaise, weight loss, hepatosplenomegaly, generalized lymphadenopathy and oral thrush, slight elevation of liver enzymes, impaired liver function, leukocytopenia, anemia, hypergammaglobulinemia and markedly depressed CD4+ cell counts at 60/cmm and CD4/CD8 ratio of 0.4. Bone marrow cytology showed massive accumulation of Leishmania donovani. The patient received SG (600 mg/day) for 14 days, during which legionella pneumonia was treated with EM (1 g, q.i.d.) and CF (200 mg, b.i.d.). Severe thrombocytopenia was self-remitting. A 2nd treatment with SB began on the 55th day for 10 days. Kaposi's **sarcoma** developed and was treated with aIF and ZV. After 3 mth leishmaniasis reappeared and SB treatment was given in combination with gIF (100 ug/day), but was discontinued because of continuous fever. Treatment was then changed to PM (250 mg/day). CD4+ helper T-cell counts did not change, but CD8+ suppressor/cytotoxic T-lymphocyte counts increased after the 2nd treatment cycle and decreased during relapse. The patient returned to work, receiving PM at 300 mg every 14 days. (W102/ECW)

L181 ANSWER 33 OF 40 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1991-44655 DRUGU M T S E

TITLE: Pneumocystis carinii Pneumonia Developing Within One Month of Intensive **Chemotherapy** for Treatment of Acute Lymphoblastic **Leukemia.**
AUTHOR: Kritz A; Sepkowitz K; Weiss M; Telford P; Sogoloff H; Kempin S
LOCATION: New York, New York, United States
SOURCE: N.Engl.J.Med. (325, No. 9, 661-62, 1991) 3 Ref.
CODEN: NEJMAG ISSN: 0028-4793
AVAIL. OF DOC.: Memorial Sloam-Kettering Cancer Center, New York, NY 10021, U.S.A. (8 authors).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1991-44655 DRUGU M T S E
AB A letter describes a case of Pneumocystis carinii pneumonia that developed within 1 mth of intensive **chemotherapy** (prednisone, vincristine, idarubicin, cytarabine, intrathecal methotrexate) for treatment of acute lymphoblastic **leukemia** (ALL). Trimethoprim + sulfamethoxazole was administered but later changed to pentamidine because of a rash. Her symptoms and chest film subsequently cleared over the next 2 wk.
ABEX A 49-yr-old HIV-negative women with ALL in whom respiratory distress with bilateral interstitial pulmonary infiltrates developed 28 days after the start of **chemotherapy** (and 14 days after the discontinuation of the 14-day course of prednisone). The protocol included prednisone (60 mg/sq.m on days 1 through 14), vincristine (2 mg/sq.m on days 1, 8 and 15), idarubicin (12 mg/sq.m on days 3 through 5), cytarabine (1 g/sq.m b.i.d. on days 3 through 7) and methotrexate (6 mg/sq.m on days 3 and 5). The diagnosis of P. carinii was made. Trimethoprim + sulfamethoxazole was added to the patient's regimen (and later changed to pentamidine because of a rash), and her symptoms and chest film cleared over the next 2 wk. (JW)

L181 ANSWER 34 OF 40 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1991-38442 DRUGU M T S E
TITLE: Low-Dose **Chemotherapy** with Central Nervous System Prophylaxis and Zidovudine Maintenance in AIDS-Related **Lymphoma.** A Prospective Multi-Institutional Trial.
AUTHOR: Levine A M; Wernz J C; Kaplan L; Rodman N; Cohen P; Metroka C
LOCATION: California, New York, North Carolina, Columbia,District, Pennsylvania, Maryland, United States
SOURCE: J.Am.Med.Assoc. (266, No. 1, 84-88, 1991) 1 Fig. 2 Tab. 32 Ref.
CODEN: JAMAAP ISSN: 0098-7484
AVAIL. OF DOC.: University of Southern California School of Medicine, 1975 Zonal Ave., KAM 110F, Los Angeles, CA 90033, U.S.A. (16 authors).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1991-38442 DRUGU M T S E
AB The effects of low dose M-BACOD (i.v. bleomycin, i.v. doxorubicin, i.v. cyclophosphamide, i.v. vincristine sulfate, p.o. dexamethasone and i.v. methotrexate with p.o. folinate calcium rescue) with intrathecal cytarabine, radiotherapy and p.o. zidovudine were investigated in 42 patients with AIDS related **lymphoma** in a phase-II trial. Pneumocystis carinii pneumonia (PCP) prophylaxis included p.o. sulfadoxine (sulformetoxine) + pyrimethamine, inhaled pentamidine

isetionate, dapsone and p.o. sulfamethoxazole + trimethoprim. Side-effects included neutropenia, granulocytopenia, neutropenic fever and sepsis (causing death). Infections included PCP (causing death), cytomegalovirus pneumonia and esophageal candidiasis. The regimen was associated with durable remission.

ABEX Methods 42 Patients (1 woman, aged 21-66 yr, median age 37 yr) with AIDS related **lymphoma** received i.v. bleomycin 4 mg/sq.m, doxorubicin 25 mg/sq.m, cyclophosphamide 300 mg/sq.m, vincristine sulfate 1.4 mg/sq.m, methotrexate 500 mg/sq.m with p.o. folinate 25 mg/6 hr rescue and p.o. dexamethasone 3 mg/sq.m. CNS prophylaxis consisted of intrathecal cytarabine 50 mg/day on days 1, 8, 21 and 28 and radiotherapy and p.o. zidovudine 200 mg/4 hr for 12 mth. PCP prophylaxis included p.o. sulfadoxine and pyrimethamine 500 mg/wk for 18 subjects, inhaled pentamidine isethionate 300 mg/mth for 11 subjects, p.o. dapsone 25 mg q.i.d. for 3 subjects or p.o. sulfamethoxazole + trimethoprim for 2 subjects. Results 18 Patients (51%) achieved a response, including 15 with CR and 3 with PR. The total number of cycles administered was 128.60% of patients experienced granulocytopenia. 12% Of cycles were delayed due to neutropenia in 21% of patients. Neutropenic fever occurred in 57% of patients with sepsis in 12% (causing death in 1 patient). PCP occurred in 9/42 patients including 3 with cytomegalovirus pneumonia and 1 with esophageal candidiasis. 7 Patients died of PCP. Median survival for all 42 subjects was 5.6 mth, 6.5 mth in 35 patients evaluable for response and 15 mth in patients with CR. Lower concentration of CD4 cells, history of prior AIDS, bone marrow involvement and stage IV disease were independently associated with decreased survival. (AJ)

=> d iall abeq tech abex 35-40
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, DRUGU, WPIX' -
CONTINUE? (Y)/N:y

L181 ANSWER 35 OF 40 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-697477 [66] WPIX
DOC. NO. CPI: C2003-191771
TITLE: Combating diseases caused by elevated levels of von Willebrand factor and/or expression of P-selectin, e.g. thrombosis or inflammation, using sodium-dependent chloride-bicarbonate exchanger inhibitors.
DERWENT CLASS: B03 B05 C02 C03
INVENTOR(S): KLEEMANN, H; LANG, H; NIEMEYER, A; OBERLEITHNER, H; SCHNEIDER, S W
PATENT ASSIGNEE(S): (AVET) AVENTIS PHARMA DEUT GMBH
COUNTRY COUNT: 102
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2003068224	A2	20030821	(200366)*	GE	82	A61K031-4174
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW						
DE 10206354	A1	20030828	(200366)			A61K031-155

AU 2003208792 A1 20030904 (200428) A61K031-4174
EP 1476154 A2 20041117 (200475) GE A61K031-4174
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003068224	A2	WO 2003-EP1100	20030205
DE 10206354	A1	DE 2002-10206354	20020214
AU 2003208792	A1	AU 2003-208792	20030205
EP 1476154	A2	EP 2003-706428	20030205
		WO 2003-EP1100	20030205

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003208792	A1 Based on	WO 2003068224
EP 1476154	A2 Based on	WO 2003068224

PRIORITY APPLN. INFO: DE 2002-10206354 20020214
INT. PATENT CLASSIF.:
MAIN: A61K031-155; A61K031-4174
SECONDARY: A61K031-166; A61K031-1666; A61K031-381; A61K031-3811; A61K031-402; A61K031-4022; A61K031-4164; A61K031-435; A61K031-4355; A61K031-4439; A61K031-44399; A61K031-47; A61K031-477; A61K031-495; **A61K031-496**; A61K031-4966; **A61K031-538**; A61K031-5388

BASIC ABSTRACT:

WO2003068224 A UPAB: 20031014

NOVELTY - Use of sodium-dependent chloride-bicarbonate exchanger (NCBE) inhibitors (I) in the production of medicaments for the prophylaxis and therapy of acute or chronic diseases caused by elevated levels of von Willebrand factor (vWF) and/or elevated expression of P-selectin, is new.

ACTIVITY - Anticoagulant; Thrombolytic; Vasotropic; Cardiant; Cerebroprotective; Antiinflammatory; Immunosuppressive; Antiarteriosclerotic; Cytostatic; Antiarthritic; Antirheumatic.

MECHANISM OF ACTION - NCBE Inhibitor; vWF Release Inhibitor; P-Selectin Expression Inhibitor.

(I) Inhibit excessive release of vWF from endothelial cells (especially the pH-dependent, massive release of vWF accumulated during ischemia), by inhibiting extracellular acidosis. In tests in umbilical venous epithelial cells cultured in an acidotic medium (pH 6.4; simulating ischemia) then in a normal medium (pH 7.4; simulating reperfusion), 4'-(5-formyl-4-(2-methoxyethoxy)-2-phenyl-1-imidazolylmethyl)-3'-methylsulfonyl-biphenyl-2-sulfonylcyanamide (Ia) at 10 micro M reduced the reperfusion-induced increase in vWF secretion by around 50 %.

USE - The diseases to be prevented or treated are specifically: thrombotic diseases caused by ischemia followed by reperfusion, e.g. thrombosis associated with acute myocardial, mesenterial or cerebral infarction; thrombotic diseases occurring during or after surgical intervention; pulmonary embolism; deep vein thrombosis, e.g. due to prolonged reduction of blood flow to the lower extremities due to prolonged lying or sitting; inflammatory diseases, e.g. as occurring during ischemia and subsequent reperfusion or during vasculitis (e.g. due to autoimmune disease or collagenosis) or initial inflammatory reactions; arteriosclerosis; cancer; or joint inflammation and arthritic diseases, e.g. rheumatoid arthritis (claimed). (I) May be used in human or

veterinary medicine.

ADVANTAGE - Unlike conventional antithrombotic agents, (I) act only on the ischemia tissue in the subsequent reperfusion phase (i.e. have no effect on pre-ischemic cells). (I) are also free of the risks of dangerous bleeding complications associated with lysis therapy.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B07-D09; B07-H; B10-A15; B14-C03; B14-C06; B14-C09; B14-F02D; B14-F04; B14-F07; B14-G02; **B14-H01**; B14-J01A4; C07-D09; C07-H; C10-A15; C14-C03; C14-C06; C14-C09; C14-F02D; C14-F04; C14-F07; C14-G02; **C14-H01**; C14-J01A4

TECH UPTX: 20031014

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: (I) Are selected from three general classes of N-cyano-benzenesulfonamide compounds (including their stereoisomers, stereoisomer mixtures and/or salts), e.g. of formula (I').

X = 2-(R1)-4-(R2)-5-(R3)-1H-imidazol-1-ylmethyl, -CR7R8-CR4R5R6 or -CR11R12-N(R10)-ZR9;
R1 = H, alkyl, -CaH2a-Ph', -CbH2b-Het or -CdH2d-cycloalkyl;
Ph' = phenyl (optionally substituted by 1-3 Q1);
Het = 1-9C heteroaryl (optionally substituted by 1-3 Q1);
a, b, d = 0-2;
Q1 = halo, CF3, Me; OMe, OH, NH2, NHT or NT2;
R2, R3 = H, halo, CF3, CN, NO2, CH2OR23, COR24, OR25, alkyl, cycloalkyl, -CaH2a-Ph', -CbH2b-Het or SOdR37;
R23 = H or alkyl;
R24 = H, alkyl, OH, alkoxy or Ph';
R25 = H, alkyl, Ph' or Het;
R37 = alkyl, cycloalkyl or Ph';
R4 = H, alkyl, 1- or 2-naphthyl, -CdH2d-cycloalkyl or -CaH2a-Ph''; or
CR4R6 = 3-7C cycloalkylidene or fluorenylidene;
Ph'' = phenyl (optionally substituted by 1-3 Q2);
Q2 = alkyl, halo, CF3, SOdR48, OH, OT, NH2, NHT, NT2, CN, NO2 or COR52;
R48 = T, NH2, NHT or NT2;
R52 = H, alkyl, OH, or alkoxy;
R5-R8 = H, F, CF3, OR56, alkyl, cycloalkyl or -CaH2a-Ph'; or
R5+R7 = additional C-C bond;
R56 = H, alkyl, Ph' or Het;
R9 = alkyl, alkenyl, -ClH2l-A or -ClH2l-m-A ;
R10 = H, alkyl, alkenyl or -ClH2l-m-B;
m = 0 or 2;
l = 0-4;
A, B = 6-14C aryl (preferably phenyl or 1- or 2-naphthyl) (optionally substituted by 1-3 Q2), Het, cycloalkyl or OR70;
R70 = H, alkyl, -ClH2l-m-Ph'' or alkenyl;
R13-R15 = H, alkyl, halo, CF3, CN, NO2, SOdR79, COR80 or OR81;
R79 = alkyl or Ph';
R80 = H, alkyl, OH or alkoxy;
R81 = H, alkyl or Ph';
Y = direct bond, CR16R17, CO, S, SO2, O or NR18;
R16 = H, OH, alkoxy or OCOR86;
R86 = alkyl or phenyl (optionally substituted by 1-3 halo, CF3, Me, OMe or OH);
R17 = H or alkyl;
R18 = H, alkyl, COR87 or SO2R87; and
R87 = alkyl, 3-8C cycloalkyl or phenyl (optionally substituted by 1-3 halo, CF3, Me, OMe or OH);
provided that:

(i) l is not 0 or 1 if m = 2; and
(ii) unless specified otherwise alkyl moieties have 1-8C, alkenyl moieties 2-8C and cycloalkyl moieties 3-7C.

ABEX UPTX: 20031014

SPECIFIC COMPOUNDS - Use of 2 compounds (I) is specifically claimed, i.e. 4'-(5-formyl-4-(2-methoxyethoxy)-2-phenyl-1-imidazolylmethyl)-3'-methylsulfonyl-biphenyl-2-sulfonylcyanamide (Ia) and 4'-((benzyl-(thiophene-2-sulfonyl)-amino)-methyl)-3'-methanesulfonyl-biphenyl-2-sulfonylcyanamide (Ib).

ADMINISTRATION - (I) Are administered orally, by inhalation, rectally, transdermally or by subcutaneous, intraarticular, intraperitoneal or intravenous injection, optionally in **combination** with (a) sodium-hydrogen exchanger (NHE) inhibitors (especially cariporide) and/or (b) blood coagulation inhibiting, platelet aggregation inhibiting or fibrinolytic agents, specifically factor Xa inhibitors, standard heparin, low molecular heparins (e.g. enoxaparin, dalteparin, certroparin, parnaparin or tinzaparin), direct thrombin inhibitors (e.g. hirudin), aspirin, fibringen receptor antagonists, streptokinase, urokinase and/or tissue plasminogen activator) (claimed). Oral administration is preferred. Dosage is 0.01-25 (preferably 0.01-5) mg/kg/day orally or 0.001-5 (preferably 0.001-2.5) mg/kg/day parenterally.

L181 ANSWER 36 OF 40 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-201249 [19] WPIX
DOC. NO. CPI: C2003-051094
TITLE: New pyrazole derivatives useful for treating e.g. cancer.
DERWENT CLASS: B02
INVENTOR(S): BEIGHT, D W; CIAPETTI, P; DECOLLO, T V; GODFREY, A G; GOODSON, T; HERRON, D K; LI, H; LIAO, J; MCMILLEN, W T; MILLER, S C; MORT, N A; SAWYER, J S; SMITH, E C R; YINGLING, J M; GOODSON, T J; BEIGHT, D; DECOLLO, T; MCMILLEN, W; SAWYER, J
PATENT ASSIGNEE(S): (ELIL) LILLY & CO ELI; (BEIG-I) BEIGHT D; (DECO-I) DECOLLO T; (GODF-I) GODFREY A G; (GOOD-I) GOODSON T; (LIHH-I) LI H; (MCMI-I) MCMILLEN W; (MILL-I) MILLER S C; (SAWY-I) SAWYER J; (SMIT-I) SMITH E C R; (YING-I) YINGLING J M
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2002094833	A1	20021128	(200319)*	EN	154	C07D487-04
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW						
NO 2003005193	A	20031121	(200407)			C07D487-04
EP 1397364	A1	20040317	(200420)	EN		C07D487-04
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR						
BR 2002009939	A	20040330	(200424)			C07D487-04
KR 2003097895	A	20031231	(200427)			C07D487-04
US 2004106604	A1	20040603	(200436)			A61K031-542
CZ 2003003128	A3	20040616	(200441)			C07D487-04
AU 2002339268	A1	20021203	(200452)			C07D487-04

CN 1511157	A	20040707	(200467)		C07D487-04
MX 2003010630	A1	20040301	(200475)		A61K031-33
SK 2003001416	A3	20041103	(200475)		C07D487-04
JP 2004535404	W	20041125	(200477)	515	C07D471-04
HU 2004000451	A2	20041228	(200506)		C07D487-04

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002094833	A1	WO 2002-US11884	20020513
NO 2003005193	A	WO 2002-US11884	20020513
		NO 2003-5193	20031121
EP 1397364	A1	EP 2002-744115	20020513
		WO 2002-US11884	20020513
BR 2002009939	A	BR 2002-9939	20020513
		WO 2002-US11884	20020513
KR 2003097895	A	KR 2003-715226	20031121
US 2004106604	A1	WO 2002-US11884	20020513
		US 2003-477111	20031106
CZ 2003003128	A3	WO 2002-US11884	20020513
		CZ 2003-3128	20020513
AU 2002339268	A1	AU 2002-339268	20020513
CN 1511157	A	CN 2002-810508	20020513
MX 2003010630	A1	WO 2002-US11884	20020513
		MX 2003-10630	20031119
SK 2003001416	A3	WO 2002-US11884	20020513
		SK 2003-1416	20020513
JP 2004535404	W	JP 2002-591506	20020513
		WO 2002-US11884	20020513
HU 2004000451	A2	WO 2002-US11884	20020513
		HU 2004-451	20020513

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1397364	A1	Based on	WO 2002094833
BR 2002009939	A	Based on	WO 2002094833
CZ 2003003128	A3	Based on	WO 2002094833
AU 2002339268	A1	Based on	WO 2002094833
MX 2003010630	A1	Based on	WO 2002094833
SK 2003001416	A3	Based on	WO 2002094833
JP 2004535404	W	Based on	WO 2002094833
HU 2004000451	A2	Based on	WO 2002094833

PRIORITY APPLN. INFO: US 2001-293464P 20010524

INT. PATENT CLASSIF.:

MAIN: A61K031-33; A61K031-542; C07D471-04; C07D487-04

SECONDARY: A61K031-41; A61K031-4439; A61K031-444; A61K031-4709; A61K031-4745; **A61K031-496**; A61K031-535; **A61K031-538**; A61K031-5383; A61K031-55; A61K045-00; A61P003-10; A61P007-04; A61P009-10; A61P013-12; A61P017-02; A61P017-12; A61P019-02; A61P021-02; A61P025-28; A61P027-02; A61P029-00; A61P031-00; A61P031-18; A61P035-00; A61P037-02; A61P037-08; A61P043-00; C07D401-12; C07D491-04; C07D498-04

BASIC ABSTRACT:

WO 200294833 A UPAB: 20031107

NOVELTY - Pyrazole derivatives are new.

DETAILED DESCRIPTION - Pyrazole derivatives of formula (I), their salts, esters or prodrugs are new.

A = 4 - 6 membered saturated ring;

R1 and R2 = e.g. phenyl, pyridine, pyridine N-oxide, quinoline (all optionally substituted);

X = C, O or S;

k = 1 - 8;

R3 = e.g. at least one H, 1-4C alkyl, 1-4C alkylhydroxy, OH or N,N-di(1-4C)alkylamino(1-4C)alkoxy.

Full definitions are given in the Definition (Full Definitions) section.

INDEPENDENT CLAIMS are also included for the following:

(1) Use of (I), their salts, esters or prodrugs, optionally in **combination** with an anti-cancer agent in the manufacture of a medicament for the treatment of cancer, fibrosis, restenosis, wound healing, HIV infection, Alzheimer's disease and/or atherosclerosis; and

(2) 3-Bromo-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo(1,2-b)pyrazole is new.

ACTIVITY - Cytostatic; Vasotropic; Vulnerary; Anti-HIV; Nootropic; Neuroprotective; Antiarteriosclerotic; Nephrotropic; Antidiabetic; Ophthalmological; Dermatological; Immunosuppressive; Respiratory-Gen.; Antiinflammatory; Antiallergic; Antirheumatic; Antiarthritic.

MECHANISM OF ACTION - Transforming growth factor-beta (TGF-beta) signal transduction inhibitors.

Cell pellets of Type I (RIT204D) receptor were lysed in lysis buffer after 48 - 72 hours of infection. The cell lysates were centrifuged, filtered and purified. Reaction was started by adding adenosine triphosphate (ATP) mix to an enzyme (170 - 200 nM) in 7-methanesulfonyl-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo(1,2-b)pyrazol-3-yl)-quinoline (A) (20 micro M - 1 nM) with 4% dimethylsulfoxide (DMSO). The reaction was incubated at 30 deg. C for 1 hour. (A) had an IC50 of less than 20 micro M.

USE - Compound (I) is used in the treatment of human or animal body therapy and in the manufacture of a medicament for the treatment of cancer, fibrosis, restenosis, wound healing, HIV infection, Alzheimer's disease and/or atherosclerosis (claimed). Also useful as intermediates for the preparation of additional compounds; for the treatment of fibroproliferative diseases such as kidney disorder, glomerulonephritis, diabetic retinopathy, renal interstitial fibrosis, renal fibrosis, progressive systemic sclerosis, pulmonary fibrosis, scleroderma, dermatomyositis, eosinophilic fasciitis, morphea, Raynaud's syndrome, adult respiratory distress syndrome, idiopathic pulmonary fibrosis, interstitial pulmonary fibrosis associated with autoimmune disorder such as systemic lupus erythematosus, chemical contact, allergies and rheumatoid arthritis.

ADVANTAGE - The compounds are potent inhibitors of TGF beta.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-H; B07-D04; B07-D08; B07-D09; B07-D10; B14-A02B1; B14-C09B; B14-F01E; B14-F01G; B14-F07; B14-G02D; **B14-H01**; B14-J01A4; B14-J05A; B14-K01; B14-K01F; B14-L06; B14-N03; B14-N10; B14-N17B; B14-N17C; B14-S04

TECH UPTX: 20031107

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) involves cyclization of substituted alkylideneamino-pyrrolidin-2-one of formula (II).

ABEX UPTX: 20031107

SPECIFIC COMPOUNDS - 374 Compounds are specifically claimed as (I), including 7-methanesulfonyl-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo(1,2-b)pyrazol-3-yl)-quinoline.

ADMINISTRATION - The dosage is 0.5 - 300 (preferably 0.5 - 20) mg/kg. The dosage is 5 - 500 (preferably 5 - 50) mg for parenteral or inhalation administration. The dosage is 25 - 500 mg for oral or rectal administration. (I) is administered orally, intramuscularly, intravenously, transdermally, rectally, topically, parenterally (including by injection).
EXAMPLE - To a solution of 4-(2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo(1,2-b)pyrazol-3-yl)-quinoline (133 mg) in dichloromethane was added m-chloroperoxybenzoic acid (248 mg) and the resulting mixture was stirred for 3 hours. The mixture was diluted, washed, dried, filtered and concentrated to obtain 7-methanesulfonyl-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo(1,2-b)pyrazol-3-yl)-quinoline (140 mg; yield 96%).

DEFINITIONS - Full Definitions:
A = 4 - 6 membered saturated ring;
X = C, O or S;
R1 = phenyl, pyridine, pyridine N-oxide, quinoline, quinoline N-oxide, naphthyridine, pyrazine, thiazolyl, imidazolyl, pyrazolyl, thiophenyl (all optionally substituted by at least one T1, hydroxymethyl, 1-4C dialkylaminomethyl, methoxyphenyl or amino) or furyl;
T1 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C alkoxy, 2-6C alkenyloxy, 2-6C alkynyloxy, 1-6C alkylthio, 1-6C alkylsulphinyl, 1-6C alkylsulphonyl, 1-6C alkylamino, di-((1-6C)alkyl)amino, 1-6C alkoxycarbonyl, N(1-6C)alkylcarbamoyl, N,N-di((1-6C)alkyl)carbamoyl, 2-6C alkanoyl, 2-6C alkanoyloxy, 2-6C alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, 3-6C alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, 3-6C alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di((1-6C)alkyl)sulphamoyl, 1-6C alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, carboxamide, ethylene, thiophenyl, aminophenyl, trifluoromethyl, halo, trifluoromethoxy, N-pyrrolidino, N-morpholino, phenylthio, OH, carboxyl, phenyl or arylalkyl;
R2 = phenyl, pyridine, pyridine N-oxide, quinoline, quinoline N-oxide, naphthalene, quinazoline, cinnoline, benzodioxole, benzodioxane, pyrimidine, benzothiophene or phenanthrolene (all optionally substituted by at least one T1, 1-6C alkylhalide, aminooxy, N-(1-6C)alkylaminooxy, N,N-di((1-6C)alkyl)aminooxy, sulphamoyl, cyano, pyridinyl, (5-phenyl-1,2,4-oxadiazole-3-yl)methoxy, 6-methyl-pyridazin-3-yloxy, (5-oxo-2-pyrrolidinyl)methoxy, 2-(4,5-dihydro-1H-imidazolyl, N,N-dialkylcarbamoyloxy, 1-hydroxy-1-methylethyl, 4-fluorophenyl or 3,4-methylenedioxyphenyl) or -X1-(CH2)n-C(R10)(R16)-(CH2)mQ1;
X1 = O, N, S, SO2, NR13, C(O) or bond;
Q1 = H, phenyl, 5-(2,2-difluoro-1,3-benzodioxolyl), C(O)Q5, pyridyl, OR11, NR11R12, halo, N-morpholino, N-piperazino-N'R13, N-imidazolyl, N-pyrazolyl, N-triazolyl, N-(4-piperidinylpiperidine), SO2R14, SOR14, NHSO2R15, acetamido, N-phthalimido, N-oxazolidino, N-benzoxazolidino, N-pyrolidinonyl, N(N'-methylbenzimidazolino), N,N-di(1-4C)alkylamino(1-4C)alkoxy or N-benzimidazolino;
Q5 = OH, methoxy, amino, diethylamino, or dimethylamino;
R10 = H, halo, or 1-6C alkyl;
R11 and R12 = H, 1-6C alkyl, 1-6C alkoxy, arylalkyl, 3-8C cycloalkyl, 3-8C cycloalkylmethyl, 4-(N-methylpiperidinyl) or pyridyl;
R11+R10 = 4 - 7 membered ring;
R11+R12, R21+R22 and R24+R25 = 3 - 7 membered ring;
R13 = H, 1-6C alkyl, 2-methoxyphenyl, or 2-pyridimidinyl;
R14 = 2-pyrimidinyl, N-methyl-2-imidazolyl, 4-chlorophenyl or

2-pyridylmethyl;
R15 = 1-6C alkyl, N-methyl-4-imidazolyl;
R16 = H, halo, arylalkyl, aryl or -C(=O)-N(R20)-(CH2)o-C(R21)(R22)-(CH2)pQ2;
Q2 = H, 4-imidazolyl, C(O)NR24R25, OR23, NR24R25 or N-morpholino;
m, n, o and p = 0 - 2;
R20, R21, R23, R24, R30, R40 - R42 = H or 1-6C alkyl;
R22 = H, 1-6C alkyl, arylalkyl or aryl;
R24+R20 = 6 or 7 membered ring;
R25 = H, 1-6C alkyl or acetyl or -C(=O)N(R30)(R31);
R31 = H, 1-6C alkyl, 2-pyridyl, pyridylmethyl, amino, OH or -NR32R33;
R32 and R33 = H, 1-6C alkyl, acetyl, 1-4C alkylsulphonyl;
R32+R33 = 4 - 7 membered ring or -N(R35)-C(=O)X2(CH2)qQ3;
X2 = CH2, O or N;
q = 0 - 3;
Q3 = bond, NR36R37 or OR38;
R35 = H;
R35+Q3 = 5 membered ring;
R36 - R38 = H, 1-6C alkyl or -O-phenyl (substituted by X3);
X3 = cyano, carboxamide, N,N-dimethylcarboxamide, N,N-dimethylthiocarboxamide, N,N-dimethylaminoethyl, 4-methylpiperazin-1-yl-methyl, carboxylate or -O-C(=O)-N(R40)(CH2)rQ6;
Q6 = NR41R42;
r = 2 - 3;
R41+R42 = 6 or 7 membered ring or CH-2-CH-CH2-C(=O)Q7;
Q7 = OH, methoxy, dimethylamino or N-piperidinyl;
k = 1 - 8;
R3 = at least one H, 1-4C alkyl, 1-4C alkylhydroxy, OH, N,N-di(1-4C)alkylamino(1-4C)alkoxy, benzyl oxymethyl, phenyloxymethyl, oxo, carboxyl, 1-4C alkylaryl, benzyloxy, acetoxy, amino(1-4C)alkyl, 2-4C alkenyl, halo, -O-(1-4C)alkyl, chlorophenethyl, acetonitrile, optionally substituted phenyl (all optionally substituted by 1-6C alkoxy, halo, carboxy or 1-6C alkoxycarbonyl).
Provided that:
(1) When one of R1 or R2 is optionally substituted phenyl, then the other cannot be optionally substituted phenyl or thiophen-2-yl;
(2) When R2 is quinolin-4-yl, substitution at the quinoline 7 position cannot include an (hetero)aryl or fused (hetero)aryl;
(3) m and n are not 0 **simultaneously** and o and p are not 0 **simultaneously**; and
(4) When Q3 is a bond then q is 2 or 3.

L181 ANSWER 37 OF 40 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-120349 [11] WPIX
CROSS REFERENCE: 2004-191124 [18]
DOC. NO. CPI: C2003-030953
TITLE: New substituted amine derivatives useful for the treatment of cancer.
DERWENT CLASS: B02 B03
INVENTOR(S): ADAMS, J; BEMIS, J; CHEN, G; CROGHAN, M; DIPIETRO, L; DOMINGUEZ, C; ELBAUM, D; GERMAIN, J; HUANG, Q; KIM, J L; KIM, T; OUYANG, X; PATEL, V F; SMITH, L M; TASKER, A; XI, N; XU, S; YUAN, C C; PIETRO, L D; ASKEW, B; BOOKER, S; DIPIETRO, L V; HABGOOD, G J; LI, A; NISHIMURA, N; NOMAK, R; RIAHI, B; GERMAN, J; YAUN, C C
PATENT ASSIGNEE(S): (AMGE-N) AMGEN INC; (ADAM-I) ADAMS J; (BEMI-I) BEMIS J; (CHEN-I) CHEN G; (CROG-I) CROGHAN M; (DOMI-I) DOMINGUEZ C; (ELBA-I) ELBAUM D; (GERM-I) GERMAIN J; (HUAN-I) HUANG Q; (KIMJ-I) KIM J L; (KIMT-I) KIM T; (OUYA-I) OUYANG X; (PATE-I) PATEL V F; (PIET-I) PIETRO L D; (SMIT-I) SMITH L

M; (TASK-I) TASKER A; (XINN-I) XI N; (XUSS-I) XU S;
(YUAN-I) YUAN C C

COUNTRY COUNT: 101

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2002068406	A2	20020906	(200311)*	EN	395	C07D401-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZW						
US 2003195230	A1	20031016	(200369)			A61K031-4439
US 2003203922	A1	20031030	(200372)			C07D403-02
HU 2003002719	A2	20031128	(200405)			A61K031-00
KR 2003078068	A	20031004	(200411)			C07D401-12
SK 2003000874	A3	20040302	(200419)			C07D401-00
AU 2002253890	A1	20020912	(200433)			C07D401-00
CZ 2003001883	A3	20040714	(200448)			C07D413-14
JP 2004527499	W	20040909	(200459)		659	C07D401-12
MX 2003006260	A1	20031001	(200466)			C07D401-00
ZA 2003005198	A	20040929	(200468)		411	C07D000-00
EP 1467721	A2	20041020	(200469)	EN		A61K031-00
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR						

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2002068406	A2		WO 2002-US3064	20020111
US 2003195230	A1	Provisional	US 2001-261882P	20010112
		Provisional	US 2001-323808P	20010919
			US 2002-46622	20020110
US 2003203922	A1	Provisional	US 2001-261882P	20010112
		Provisional	US 2001-323808P	20010919
		CIP of	US 2002-46622	20020110
			US 2002-197918	20020717
HU 2003002719	A2		WO 2002-US3064	20020111
			HU 2003-2719	20020111
KR 2003078068	A		KR 2003-709276	20030711
SK 2003000874	A3		WO 2002-US3064	20020111
			SK 2003-874	20020111
AU 2002253890	A1		AU 2002-253890	20020111
CZ 2003001883	A3		WO 2002-US3064	20020111
			CZ 2003-1883	20020111
JP 2004527499	W		JP 2002-567920	20020111
			WO 2002-US3064	20020111
MX 2003006260	A1		WO 2002-US3064	20020111
			MX 2003-6260	20030711
ZA 2003005198	A		ZA 2003-5198	20030704
EP 1467721	A2		EP 2002-723086	20020111
			WO 2002-US3064	20020111

FILING DETAILS:

PATENT NO	KIND	PATENT NO

HU 2003002719	A2	Based on	WO 2002068406
SK 2003000874	A3	Based on	WO 2002068406
AU 2002253890	A1	Based on	WO 2002068406
CZ 2003001883	A3	Based on	WO 2002068406
JP 2004527499	W	Based on	WO 2002068406
MX 2003006260	A1	Based on	WO 2002068406
EP 1467721	A2	Based on	WO 2002068406

PRIORITY APPLN. INFO: US 2002-46622 20020110; US
2001-261882P 20010112; US
2001-323808P 20010919; US
2002-197918 20020717

INT. PATENT CLASSIF.:
MAIN: A61K031-00; A61K031-4439; C07D000-00; C07D401-00; C07D401-12; C07D403-02; C07D413-14
SECONDARY: A61K031-165; A61K031-401; A61K031-4025; A61K031-403; A61K031-416; A61K031-44; A61K031-4427; A61K031-444; A61K031-4523; A61K031-454; A61K031-4545; A61K031-4709; A61K031-4725; A61K031-4745; **A61K031-496**; A61K031-517; A61K031-5377; **A61K031-538**; A61P001-04; A61P001-16; A61P003-04; A61P007-06; A61P009-00; A61P009-10; A61P011-00; A61P011-06; A61P015-00; A61P017-02; A61P017-06; A61P019-02; A61P027-02; A61P027-06; A61P029-00; A61P031-12; A61P031-18; A61P035-00; A61P035-02; A61P035-04; A61P037-02; A61P037-08; A61P043-00; C07D213-56; C07D231-56; C07D401-02; C07D401-14; C07D405-12; C07D405-14; C07D407-12; C07D409-14; C07D413-12; C07D417-04; C07D417-12; C07D417-14; C07D471-04

BASIC ABSTRACT:

WO 200268406 A UPAB: 20041027

NOVELTY - Substituted amine derivatives (I) are new.

DETAILED DESCRIPTION - Substituted amine derivatives of formula (I) are new:

A1, A2 = C, CH or N;

A = partially saturated 5-6 membered heterocyclyl, 5-6 membered heteroaryl, partially saturated 9-11 membered fused heterocyclyl, 9-11 membered fused heteroaryl, aryl, or 4-6 membered cycloalkenyl;

X = -C(=Z)-N(R5a)-R4-;

Z = O or S;

R = 4-6 membered heterocyclyl, aryl or fused 9-14 membered bicyclic or tricyclic heterocyclyl (all optionally substituted by at least one lower alkyl, lower alkenyl, lower alkynyl (all substituted by R2), halo, -OR3, -SR3, -SO2R3, -CO2R3, -CONR3R3, -COR3, -NR3R3, -SO2NR3R3, -NR3C(O)OR3, -NR3C(O)R3, cycloalkyl, optionally substituted 3-6 membered heterocyclyl, optionally substituted phenyl, nitro, alkylaminoalkoxyalkoxy, CN, oxo or alkylaminoalkoxy);

R1 = 6-10 membered aryl, 4-6 membered heterocyclyl, 9-14 membered bicyclic or tricyclic heterocyclyl (all optionally substituted by at least one lower alkyl, lower alkenyl or lower alkynyl (all substituted by R2), cycloalkyl, 4-6 membered heterocyclyl, phenyl (all optionally substituted), halo, -OR3, -SR3 , -CO2R3, -CONR3R3 , -COR3 , -NR3R3 , -NH(1-4C alkylenylR14), -SO2R3, -SO2NR3R3, -NR3C(O)OR3, NR3C(O)R3, -NR3C(O)NR3R3, halosulfonyl, CN, alkylaminoalkoxy(alkoxy), nitro), cycloalkyl or cycloalkenyl;

R2 = phenylalkylenyl, 4-6 membered heterocyclyl, heteroarylalkylenyl, phenyl (all optionally substituted), H, halo, -OR3, oxo, -SR3, -CO2R3, -COR3, -CONR3R3, NR3R3, -SO2NR3R3, -NR3C(O)OR3, -NR3C(O)R3, cycloalkyl, lower alkyl, CN, lower hydroxyalkyl, lower carboxyalkyl, nitro, 1-6C-alkoxy-1-6C-alkoxy, 1-6C-alkoxy-1-6C-alkoxy-1-6C-alkoxy, lower

alkenyl, lower alkynyl, lower (alkyl) aminoalkyl or lower haloalkyl;

R3 = phenyl, 3-6 membered heterocyclyl, 3-6C cycloalkyl, phenylalkyl, 3-6 membered heterocyclylalkyl, 3-6C cycloalkylalkyl (all optionally substituted), H or lower (halo)alkyl;

R4 = direct bond, 2-4C-alkylenyl, 2-4C-alkenylenyl or 2-4C-alkynylenyl (all optionally replaced by O or -NH- and optionally substituted by OH);

R5 = phenyl, lower aralkyl (both optionally substituted), H or lower alkyl;

R14 = phenyl, 4 - 6 membered heterocyclyl, 3-6C cycloalkyl (all optionally substituted) or H; and

provided that:

(a) when X = -C(O)NH-, R1 = 4-(3,5-bis(trifluoromethyl)-1H-pyrazol-2-yl)phenyl, R5 = methyl and R = 4-methylpiperidyl then A is not pyridyl;

(b) when X = -C(O)NH-, R5 = H, R2 = 6-methyl and R = indazolyl then A is not pyridyl;

(c) when X = -C(O)NH-, R1 = phenyl, 4-bromophenyl, 2-methylphenyl or 4-methoxyphenyl, R5 = H and R = 4-pyridyl then A is not phenyl;

(d) when X = -C(O)NH-, R1 = phenyl, R5 = H and R = 2-oxobenzopyran-4-yl then A is not phenyl;

(e) when X = -C(O)NH-, R1 = phenyl, 4-chlorophenyl, 3-nitrophenyl or 4-methoxyphenyl, R5 = H and R = 4-imidazolinyl then A is not phenyl;

(f) when X = -C(O)NH-, R5 = H, R5a = substituted benzyl and R = substituted triazinyl then A is not phenyl;

(g) when X = -C(O)NH-, R2 = phenyl or 2-chlorophenyl, R5 = H and R = 4-quinazolinyl then A is not phenyl;

(h) when X = -C(O)NH-, R1 = phenyl, R5 = H and R = isoquinolin-1-yl then A is not phenyl;

(i) when X = -C(O)NH-, R1 is 2-chlorophenyl or 4-chlorophenyl, R5 = H and R = 3-chloroisoquinolin-1-yl then A is not phenyl;

(j) when X = -C(O)NH-, R1 = 1-ethylpiperid-3-yl or 1-ethylpiperid-4-yl, R5 = H and R = 8-trifluoromethylquinolin-4-yl then A is not phenyl;

(k) when X = -C(O)NH-, R1 = 1-ethylpiperid-3-yl, R5 = H and R = 8-chloroquinolin-4-yl then A is not phenyl;

(l) when X = -C(O)NH-, R1 = phenyl (substituted by halo), 1-butylpiperid-4-yl, 1-ethylpiperid-3-yl or 1-ethylpiperid-4-yl, R5 = H and R = 7-chloroquinolin-4-yl then A is not phenyl; and

(m) R is not unsubstituted 2-thienyl, unsubstituted 2-pyridyl or unsubstituted 3-pyridyl.

INDEPENDENT CLAIMS are also included for the following:

(1) use of (I) in the preparation of medicament for treating cancer, angiogenesis or cell proliferation; and

(2) preparation of (I).

ACTIVITY - Cytostatic; Antiinflammatory; Anti-HIV; Antidiabetic; Ophthalmological; Vasotropic; Hemostatic; Antiulcer; Gynecological; Antirheumatic; Antiarthritic; Antipsoriatic; Dermatological; Osteopathic; Antiarteriosclerotic; Antipyretic; Antithyroid; Vulnerary; Cerebroprotective; Antiallergic; Immunosuppressive; Tranquilizer; Hepatotropic; Analgesic; Antisickling; Antibacterial; Antiasthmatic; Anorectic.

MECHANISM OF ACTION - Protein Kinase Inhibitor; Vascular Endothelial Growth Factor (VEGF) Inhibitor. N-(4-Chlorophenyl)(2-(1H-indazol-6-ylamino)(3-pyridyl))carboxamide (I') inhibited VEGF-stimulated human umbilical vein endothelial cell (HUVEC) proliferation at a level below 50 nM.

USE - For treating cancer, angiogenesis, KDR-related disorders, proliferation-related disorders (e.g. inflammation or an inflammation-related disorder) in human or animal body, as antineoplasia agents (claimed). Also, for treating hematopoietic tumors of lymphoid,

myeloid or mesenchymal lineage, tumors of the central and peripheral nervous system, other tumors (e.g. melanoma or Kaposi's sarcoma), ophthalmological conditions (e.g. corneal graft rejection, diabetic retinopathy or neovascular glaucoma), retinal ischemia, vitreous hemorrhage, ulcerative diseases, pathological but non-malignant conditions, disorders of the female reproductive system, edema, conditions of vascular hyperpermeability, rheumatoid arthritis, psoriasis, arthropathy, paraneoplastic syndrome, tumor-induced inflammatory diseases, turbid effusions, collagenosis (e.g. systemic lupus erythematosus), postinfectious arthritis, seronegative spondyloarthritis, vasculitis, sarcoidosis, synovial inflammation (e.g. osteoarthritis), insertion endopathy, myofasciale syndrome, tendomyosis, inflammatory disease or condition of connective tissues (e.g. dermatomyositis), atherosclerosis, psoriasis, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb angiogenesis, wound healing, peptic ulcer Helicobacter related diseases, fractures, cat scratch fever, rubeosis, thyroid hyperplasia (especially Grave's disease), cysts, burns, chronic lung disease, stroke, polyps, anaphylaxis, chronic and allergic inflammation, ovarian hyperstimulation syndrome, cerebral edema, for treating disorders in which protein extravasation leads to the deposition of fibrin and extracellular matrix, promoting stromal proliferation (e.g. fibrosis, cirrhosis and carpal tunnel syndrome), stromal deposition occurs in viral infections, radiation, Crohn's disease, sickle cell anemia, Lyme disease, pemphigoid, Paget's disease, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic occlusive pulmonary disease, asthma, reduction of fat, obesity, retinoblastoma, rhabdomyosarcomas, neuroblastoma or microangiopathy.

ADVANTAGE - (I) Minimize deleterious effects of VEGF.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-H; B07-H; B14-C03; B14-C04; B14-C09; B14-D01; B14-E08; B14-E12; B14-F02D1; B14-F02F1; B14-F07; B14-G02A; B14-G02B; **B14-H01**; B14-K01; B14-N01; B14-N03; B14-N11; B14-N14; B14-N16; B14-P02; B14-S04

TECH UPTX: 20030214

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (Claimed): Preparation of (I) involves reacting a compound of formula (II) with R1R4-NH2 in presence of base and an inert solvent followed by coupling with a primary or secondary amine HNR5R.

LG = leaving group.

Preferred Compounds: Substituted amine derivatives are of formula (Ia)-(Ii).

A3, A4, A6 = CR'2 or N;

A5 = S, O or NR'6;

R' = 9-10 membered fused nitrogen containing heteroaryl (preferably indazolyl) (optionally substituted by at least one T (preferably T');

T = halo, amino, OH, 1-6C alkyl, 1-6C haloalkyl, 1-6C alkoxy, optionally substituted heterocyclylalkoxy, 1-6C alkylamino-2-4C alkynyl, 1-6C alkylamino-1-6C alkoxy, 1-6C alkylamino-1-6C alkoxy-1-6C alkoxy or optionally substituted heterocyclyl-2-4C alkynyl;

T' = Cl, F, OH, amino, Me, Et, Pr, trifluoromethyl, dimethylaminopropynyl, 1-methylpiperidinylmethoxy, dimethylaminoethoxyethoxy, methoxy or ethoxy;

R'1 = aryl, cycloalkyl, 5-6 membered heteroaryl, 9-10 membered bicyclic or 13-14 membered tricyclic heterocyclyl (preferably phenyl, tetrahydronaphthyl, indanyl, indenyl, naphthyl, cyclohexyl, isoxazolyl, pyrazolyl, thiazolyl, thiadiazolyl, thienyl, pyridyl, pyrimidinyl, pyridazinyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl,

isoquinolyl, quinolyl, indolyl, isoindolyl, 2,3-dihydro-1H-indolyl, naphthyridinyl, quinozalinyl, benzo(d)isothiazolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo(3,4-a)isoquinolyl, tetrahydroquinolinyl, indazolyl, 2,1,3-benzothiadiazolyl, benzodioxanyl, benzothienyl, benzofuryl, benzimidazolyl, dihydrobenzimidazolyl, benzoxazolyl or benzothiazolyl) (optionally substituted by at least one 3-6C cycloalkyl, phenyl, phenyl-1-4C alkylenyl, phenyloxy, 4-6 membered heterocyclyl-1-4C alkylenyl, 4-6 membered heterocyclyl-2-4C alkenylenyl, 4-6 membered heterocyclyl, 4-6 membered heterocyclyloxy, 4-6 membered heterocyclyl-1-4C alkoxy, 4 - 6 membered heterocyclylsulfonyl, 4-6 membered heterocyclylamino, 4-6 membered heterocyclylcarbonyl, 4-6 membered heterocyclyl-1-4C alkylcarbonyl (all optionally substituted), halo, 1-6C alkyl, 1-2C haloalkoxy, 1-2C haloalkyl, 1-4C aminoalkyl, nitro, amino, OH, CN, aminosulfonyl, 1-2C alkylsulfonyl, halosulfonyl, 1-4C alkylcarbonyl, 1-3C alkylamino-1-3C alkyl, 1-3C alkylamino-1-3C alkoxy, 1-3C alkylamino-1-3C alkoxy-1-3C alkoxy, 1-4C alkoxycarbonyl, 1-4C alkoxycarbonylamino-1-4C alkyl, 1-4C hydroxyalkyl, -C(Re)(Rf)-O-R7 or 1-4C alkoxy (preferably halo, nitro, amino, CN, aminoethyl, Boc-aminoethyl, OH, aminosulfonyl, 4-methylpiperazinylsulfonyl, cyclohexyl, phenyl, phenylmethyl, morpholinylmethyl, methylpiperazinylmethyl, methylpiperazinylpropyl, morpholinylpropyl, methylpiperidinylmethyl, morpholinylethyl, 1-(4-morpholinyl)-2,2-dimethylpropyl, piperidinylethyl, piperidinylmethyl, piperidinylpropyl, pyrrolidinylpropyl, pyrrolidinylpropenyl, pyrrolidinylbutenyl, fluorosulfonyl, methylsulfonyl, methylcarbonyl, piperidinylmethylcarbonyl, methylpiperazinylcarbonylethyl, methoxycarbonyl, 3-ethoxycarbonyl-2-methyl-furan-5-yl, methylpiperazinyl, methylpiperidyl, 1-methyl-(1,2,3,6-tetrahydropyridyl), imidazolyl, morpholinyl, 4-trifluoromethyl-1-piperidinyl, hydroxybutyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, sec-butyl, trifluoromethyl, pentafluoroethyl, nonafluorobutyl, dimethylaminopropyl, 1,1-di(trifluoromethyl)-1-hydroxymethyl, 1,1-di(trifluoromethyl)-1-(piperidinylethoxy)methyl, 1,1-di(trifluoromethyl)-1-(methoxyethoxyethoxy)methyl, 1-hydroxyethyl, 2-hydroxyethyl, trifluoromethoxy, 1-aminoethyl, 2-aminoethyl, 1-(N-isopropylamino)ethyl, 2-(N-isopropylamino) ethyl, dimethylaminoethoxy, 4-chlorophenoxy, phenyloxy, 1-methylpiperidin-4-yloxy, isopropoxy, methoxy or ethoxy);
R'2 = halo, OH, amino, 1-6C alkyl, 1-6C haloalkyl, 1-6C alkoxy, 1-2C alkylamino, aminosulfonyl, 3-6C cycloalkyl, CN, 1-2C hydroxyalkyl, nitro, 2-3C alkenyl , 2-3C alkynyl, 1-6C haloalkoxy, 1-6C carboxyalkyl, 5-6 membered heterocyclyl-1-6C alkylamino, optionally substituted phenyl or optionally substituted 4-6 membered heterocyclyl (preferably H, Cl, F, Br, amino, OH, Me, Et, Pr, oxo, dimethylamino, aminosulfonyl, cyclopropyl, CN, hydroxymethyl, nitro, propenyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl, morpholinylethylamino, propynyl, optionally substituted phenyl or optionally substituted heteroaryl selected from thienyl);
R'4 = direct bond, 1-4C alkyl or -CH2-CH(OH)-CH2-O-;
Re, Rf = H or 1-2C haloalkyl;
R7 = H, 1-3C alkyl, optionally substituted phenyl, optionally substituted phenyl-1-3C alkyl, 4-6 membered heterocyclyl, optionally substituted 4-6 membered heterocyclyl-1-3C alkyl, 1-3C alkoxy-1-2C alkyl or 1-3C alkoxy-1-3C alkoxy-1-3C alkyl;
R'6 = H or 1-6C alkyl; and
R10-R13 = -C(O)-NH-R'4-R'1, -NHR' or H;
provided that:
(a) 1 of A3 and A4 is not CR'2;
(b) when R10 = -C(O)-NH-R'4-R'1, then R11 = -NHR', R12 = H and R13 = H;
(c) when R10 = -NHR', then R11 = -C(O)-NH-R'4-R'1, R12 = H and R3 = H;
(d) when R10 = H, then R11 = -NHR', R12 = -C(O)-NH-R'4-R'1 and R13 = H;

(e) when R10 = H, then R11 = -C(O)-NH-R'4-R'1, R12 = -NHR' and R13 = H;
(f) when R10 = H, then R11 = H, R12 = -C(O)-NH-R'4-R'1 and R13 = -NHR'; and
(g) when R10 = H, then R11 = H, R12 = -NHR' and R13 = -C(O)-NH-R'4-R'1.

ABEX UPTX: 20030214

SPECIFIC COMPOUNDS - 126 Compounds (I) are specifically claimed e.g. N-(4-chlorophenyl)(2-(1H-indazol-6-ylamino)(3-pyridyl))carboxamide (I').

ADMINISTRATION - Administration of (I) is 0.01-500 (preferably 0.1-20) mg/kg/day in 1-4 doses orally, mucosally, topically, rectally, pulmonarily (including by inhalation spray) or parenterally (including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly, intrasternally or by infusion). (I) May be administered in **combination** with antibiotic-type agents, alkylating agents, antimetabolite agent, hormonal agent, immunological agent or interferon-type agent etc.

EXAMPLE - 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6 g) and hydroxybenzotriazole (3.3 g) was added to a mixture of 2-chloronicotinic acid (4 g), 4-chloroaniline (3.2 g) and diisopropylethylamine (6 ml) in CH2Cl2 (200 ml). The reaction was stirred at room temperature overnight and washed with 2 N NaOH (100 ml), H2O (150 ml) and brine (100 ml). The organic layer was dried over Na2SO4 and evaporated to give (2-chloro(3-pyridyl))-N-(4-chlorophenyl)carboxamide (A). A mixture of (A) (200 mg) and 6-aminoindazole (150 mg) was heated at 150 degrees C for 2 hours. The reaction was cooled and washed with MeOH. After work-up, N-(4-chlorophenyl)(2-(1H-indazol-6-ylamino)(3-pyridyl))carboxamide (I') was obtained.

DEFINITIONS - Preferred Definitions:
A = isoxazol-4,5-diyl, isoxazol-3,4-diyl, isothiazol-4,5-diyl, isothiazol-3,4-diyl, thiazol-4,5-diyl, oxazole-4,5-diyl, 1H-imidazol-1,5-diyl, thiophen-2,3-diyl, furan-2,3-diyl, 1H-imidazol-1,2-diyl, 1H-pyrrol-1,2-diyl, 1H-pyrazol-1,5-diyl, 1H-(1,2,4)triazol-1,5-diyl, furan-3,4-diyl, thiophen-3,4-diyl, pyridin-2,3-diyl, pyridin-3,4-diyl, pyrazin-2,3-diyl, pyridazin-3,4-diyl, pyrimidin-4,5-diyl, pyridazin-4,5-diyl, or 1H-imidazol-4,5-diyl, 1H-pyrrol-2,3-diyl 1H-pyrazol-4,5-diyl, 1H-pyrazol-3,4-diyl or 1H-pyrrol-3,4-diyl (all substituted by Rc at position 1);
X = -C(=O)-NH-;
Rc = H, methyl and optionally substituted phenyl;
R = 4-pyridyl, (heterocyclyl-substituted phenyl) (both optionally substituted by at least one piperidinyl, piperazinyl, phenyl (all optionally substituted), Cl, F, Br, OH, OMe, OEt, amino, dimethylamino, diethylamino, 1-methylpiperidinylmethoxy, aminosulfonyl, cyclohexyl, dimethylaminopropynyl, dimethylaminoethoxy, 3-(4-morpholinyl)propyn-1-yl, dimethylaminoethoxyethoxy, morpholinyl, Me, Et, Pr, CN, hydroxymethyl, aminomethyl, nitro or trifluoromethyl), 3-pyridyl, 2-pyridyl, triazolyl, 4-pyrimidinyl, 4-pyridazinyl, 5-indazolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, (iso)indolyl, benzotriazolyl, 2,3-dihydrobenzofuryl, 2-oxo-1,2-dihydroquinol-7-yl, quinozalinyl, 4-isoquinolyl, 5-isoquinolyl, naphthyridinyl or 6-isoquinolyl;
R1 = phenyl (optionally substituted by at least one halo, nitro, amino, CN, aminoethyl, Boc-aminoethyl, OH, oxo, aminosulfonyl, 4-methylpiperazinylsulfonyl, cyclohexyl, phenyl, phenylmethyl, morpholinylmethyl, 1-methylpiperazin-4-ylmethyl, 1-methylpiperazin-4-ylpropyl, morpholinylpropyl, piperidin-1-ylmethyl, 1-methylpiperidin-4-ylmethyl, 2-methyl-2-(1-methylpiperidin-4-yl)ethyl, morpholinylethyl, 1-(4-morpholinyl)-2,2-dimethylpropyl, piperidin-4-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-1-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-4-ylmethyl, 1-Boc-piperidin-4-ylmethyl, piperidin-4-ylpropyl,

1-Boc-piperidin-4-ylpropyl, piperidin-1-ylpropyl, pyrrolidin-1-ylpropyl, pyrrolidin-2-ylpropyl, 1-Boc-pyrrolidin-2-ylpropyl, pyrrolidin-1-ylmethyl, pyrrolidin-2-ylmethyl, 1-Boc-pyrrolidin-2-ylmethyl, pyrrolidinylpropenyl, pyrrolidinylbutenyl, fluorosulfonyl, methylsulfonyl, methylcarbonyl, Boc, piperidin-1-ylmethylcarbonyl, 4-methylpiperazin-1-ylcarbonylethyl, methoxycarbonyl, aminomethylcarbonyl, dimethylaminomethylcarbonyl, 3-ethoxycarbonyl-2-methyl-fur-5-yl, 4-methylpiperazin-1-yl, 4-methyl-1-piperidyl, 1-Boc-4-piperidyl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-methyl-(1,2,3,6-tetrahydropyridyl), imidazolyl, morpholinyl, 4-trifluoromethyl-1-piperidinyl, hydroxybutyl, Me, Et, Pr, i-Pr, Bu, t-Bu, sec-butyl, trifluoromethyl, pentafluoroethyl, nonafluorobutyl, dimethylaminopropyl, 1,1-di(trifluoromethyl)-1-hydroxymethyl, 1,1-di(trifluoromethyl)-1-(piperidinylethoxy)methyl, 1,1-di(trifluoromethyl)-1-(methoxyethoxyethoxy)methyl, 1-hydroxyethyl, 2-hydroxyethyl, trifluoromethoxy, 1-aminoethyl, 2-aminoethyl, 1-(N-isopropylamino)ethyl, 2-(N-isopropylamino)ethyl, dimethylaminoethoxy, 4-chlorophenoxy, phenyloxy, azetidin-3-ylmethoxy, 1-Boc-azetidin-3-ylmethoxy, pyrrol-2-ylmethoxy, 1-Boc-pyrrol-2-ylmethoxy, pyrrol-1-ylmethoxy, 1-methyl-pyrrol-2-ylmethoxy, 1-isopropyl-pyrrol-2-ylmethoxy, 1-Boc-piperidin-4-ylmethoxy, piperidin-4-ylmethoxy, 1-methylpiperidin-4-yloxy, isopropoxy, methoxy or ethoxy), indanyl, tetrahydronaphthyl, naphthyl, indazolyl, indolyl, 2,1,3-benzothiadiazolyl, cyclohexyl, isoxazolyl, pyrazolyl, thiazolyl, thiadiazolyl, thienyl, pyridyl, pyrimidinyl, pyridazinyl, ,2-dihydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, isoindolyl, 2,3-dihydro-1H-indolyl, naphthyridinyl, benzothienyl, benzofuryl, benzimidazolyl, dihydro-benzimidazolyl, benzoxazolyl, benzothiazolyl, isoquinolyl, quinolyl, tetrahydroquinolyl, benzo(d)isothiazolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-azafluorenyl, 5,6,7-trihydro-1,2,4-triazolo(3,4-a)isoquinolyl, benzodioxanyl and quinazolinyl; and
R2 = phenyl, thienyl, furanyl, pyridyl, imidazolyl or pyrazolyl (all optionally substituted), H, Cl, Br, F, OH, OMe, OEt, trifluoromethoxy, oxo, amino, dimethylamino, aminosulfonyl, carboxymethyl, cyclopropyl, Me, Et, Pr, CN, hydroxymethyl, nitro, propenyl, propynyl or trifluoromethyl.

L181 ANSWER 38 OF 40 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-732685 [79] WPIX
CROSS REFERENCE: 2004-191112 [18]
DOC. NO. CPI: C2002-207271
TITLE: New substituted arylamine derivatives are e.g. vascular endothelial growth factor receptor inhibitors, used e.g. for the treatment of cancer and angiogenesis.
DERWENT CLASS: B02 B03
INVENTOR(S): BOOKER, S; CAI, G; CHEN, G; CROGHAN, M; DIPIETRO, L; DOMINGUEZ, C; ELBAUM, D; GERMAIN, J; HUANG, Q; KIM, J L; KIM, T; PATEL, V F; SMITH, L M; TASKER, A; XI, N; XU, S; YUAN, C C; ASKEW, B; HABGOOD, G; HANDLEY, M; LI, A; NISHIMURA, N
PATENT ASSIGNEE(S): (AMGE-N) AMGEN INC; (BOOK-I) BOOKER S; (CAIG-I) CAI G; (CHEN-I) CHEN G; (CROG-I) CROGHAN M; (DIPI-I) DIPIETRO L; (DOMI-I) DOMINGUEZ C; (ELBA-I) ELBAUM D; (GERM-I) GERMAIN J; (HUAN-I) HUANG Q; (KIMJ-I) KIM J L; (KIMT-I) KIM T; (PATE-I) PATEL V F; (SMIT-I) SMITH L M; (TASK-I) TASKER A; (XINN-I) XI N; (XUSS-I) XU S; (YUAN-I) YUAN C C
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2002055501	A2	20020718	(200279)*	EN	253	C07D213-81

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZW

US	2002147198	A1	20021010	(200279)		C07D211-32
US	2003134836	A1	20030717	(200348)		C07D417-02
EP	1358161	A2	20031105	(200377)	EN	C07D213-81

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI TR

AU	2002248339	A1	20020724	(200427)		C07D213-81
MX	2003006010	A1	20031001	(200466)		A61K031-44
JP	2004531473	W	20041014	(200467)	421	C07D213-81
US	2004204437	A1	20041014	(200469)		A61K031-473

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2002055501	A2		WO 2002-US742	20020111
US 2002147198	A1	Provisional	US 2001-261360P	20010112
		Provisional	US 2001-323686P	20010919
			US 2002-46526	20020110
US 2003134836	A1	Provisional	US 2001-261360P	20010112
		Provisional	US 2001-323686P	20010919
		CIP of	US 2002-46526	20020110
			US 2002-197960	20020717
EP 1358161	A2		EP 2002-717324	20020111
			WO 2002-US742	20020111
AU 2002248339	A1		AU 2002-248339	20020111
MX 2003006010	A1		WO 2002-US742	20020111
			MX 2003-6010	20030702
JP 2004531473	W		JP 2002-556173	20020111
			WO 2002-US742	20020111
US 2004204437	A1	Provisional	US 2001-323686P	20010919
		CIP of	US 2002-46526	20020110
		Cont of	US 2002-197960	20020717
			US 2004-823809	20040412

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1358161	A2	Based on	WO 2002055501
AU 2002248339	A1	Based on	WO 2002055501
MX 2003006010	A1	Based on	WO 2002055501
JP 2004531473	W	Based on	WO 2002055501

PRIORITY APPLN. INFO: US 2002-46526 20020110; US
2001-261360P 20010112; US
2001-323686P 20010919; US
2002-197960 20020717; US
2004-823809 20040412

INT. PATENT CLASSIF.:
MAIN: A61K031-44; A61K031-473; C07D211-32; C07D213-81;
C07D417-02
SECONDARY: A61K031-4427; A61K031-443; A61K031-4436; A61K031-4439;
A61K031-444; A61K031-445; A61K031-4545; A61K031-4709;
A61K031-4725; **A61K031-496**; A61K031-498;

A61K031-50; A61K031-501; A61K031-506; A61K031-517; A61K031-5377; **A61K031-538**; A61K031-541; A61K031-55; A61P001-04; A61P003-00; A61P003-04; A61P003-10; A61P009-00; A61P009-10; A61P011-00; A61P011-06; A61P015-00; A61P015-08; A61P017-00; A61P017-02; A61P017-06; A61P019-00; A61P019-02; A61P021-00; A61P025-28; A61P027-02; A61P027-06; A61P029-00; A61P031-12; A61P031-18; A61P031-22; A61P035-00; A61P035-02; A61P035-04; A61P037-02; A61P037-04; A61P037-08; A61P043-00; C07D213-82; C07D237-02; C07D401-02; C07D401-12; C07D401-14; C07D403-02; C07D405-12; C07D409-12; C07D413-02; C07D413-12; C07D417-12

BASIC ABSTRACT:

WO 200255501 A UPAB: 20041027

NOVELTY - Substituted arylamine derivatives (I) are new.

DETAILED DESCRIPTION - Substituted arylamine derivatives of formula (I) are new;

For full definitions see Definition field.

INDEPENDENT CLAIMS are also included for:

(1) a method of treating cancer, angiogenesis, KDR-related or proliferation disorders by administering (I);

(2) the use of (I) in the manufacture of a medicament for the treatment of cancer, angiogenesis and cell proliferation; and

(3) the preparation of (I).

ACTIVITY - Cytostatic; Dermatological; Antiarteriosclerotic; Antiarthritic; Antirheumatic; Antiinflammatory; Immunosuppressive; Antitumor; Ophthalmological; Antiasthmatic; Nephrotropic; Antidiabetic; Antithyroid; Anti-HIV; Antiulcer; Antipsoriatic; Cardiant; Cerebroprotective; Antiallergic; Vulnerary; Tranquilizer; Virucide; Gynecological; Antisickling; Antibacterial; Osteopathic; Anorectic.

A431 cells (ATCC) were expanded in culture, harvested and injected subcutaneously into 5-8 week old female nude mice. Subsequent administration of compounds of formula (I) by oral gavage (10-200 mpk/dose) was performed between days 0-29 post tumor cell challenge and was continued one or two days for the duration of the experiment.

Progression of tumor growth was followed by three dimensional caliper measurements over time.

Compounds of formula (I) exhibited activity at doses less than 150 mpk.

MECHANISM OF ACTION - Vascular endothelial growth factor receptor (VEGFR) or KDR inhibitor; Protein kinase inhibitors; Angiogenesis inhibitor. N-(3,3-Dimethyl-1-(1-methyl-piperidin-4-yl)-2,3-dihydro-1H-indol-6-yl)-2-(4-fluoro-benzylamino)-nicotinamide was tested for human umbilical vein endothelial cells proliferation assay using cryopreserved cells and IC50 value was found to be below 50 nM.

No specific results were given for any particular compound of formula (I) in the specification.

USE - In the manufacture of a medicament for the treatment of angiogenesis, KDR-related disorders, proliferation-related disorders and cancer; as an active therapeutic-substance, for antineoplasia use (all claimed); neoplasia including cancer and metastasis, including carcinoma; hematopoietic tumors of lymphoid lineage (e.g. leukemias); hematopoietic tumors of myeloid lineage (e.g. myelodysplastic syndrome); tumors of mesenchymal origin (e.g. sarcomas of soft tissue and bone); tumors of the central and peripheral nervous system (e.g. astrocytoma, neuroblastoma, glioma and schwannomas); and other tumors (e.g. melanoma); for ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization (following injury or infection), diabetic retinopathy, retrolental fibroplasia and neovascular

glaucoma; retinal ischemia; vitreous hemorrhage; ulcerative diseases (e.g. gastric ulcer); hemangiomas, (e.g. angiofibroma of the nasopharynx); and disorders of the female reproductive system (e.g. endometriosis), edema and conditions of vascular hyperpermeability in therapy of proliferative diseases; inflammatory rheumatoid or rheumatic disease, especially of manifestations at the locomotor apparatus (e.g. various inflammatory rheumatoid diseases such as synovitis); paraneoplastic syndrome or tumor-induced inflammatory diseases, turbid effusions, collagenosis (e.g. systemic Lupus erythematosus); postinfectious arthritis, seronegative spondylarthritis (e.g. spondylitis ankylosans). The synovial inflammation (e.g. be consequential to or associated with disease, e.g. arthritis, osteoarthritis, rheumatoid arthritis or arthritis deformans); as active agents against such disease states as arthritis, atherosclerosis, psoriasis, hemangiomas, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb angiogenesis, wound healing, peptic ulcer Helicobacter related diseases, fractures, cat scratch fever, rubeosis, neovascular glaucoma and retinopathies such as those associated with diabetic retinopathy or macular degeneration; solid tumors, malignant ascites, hematopoietic cancers and hyperproliferative disorders such as thyroid hyperplasia and cysts (e.g. hypervascularity of ovarian stroma); burns, chronic lung disease, stroke, polyps, anaphylaxis, chronic and allergic inflammation, ovarian hyperstimulation syndrome, brain tumor-associated cerebral edema, high-altitude, trauma or hypoxia induced cerebral or pulmonary edema, ocular and macular edema, ascites, and other diseases where vascular hyperpermeability, effusions, exudates, protein extravasation, or edema is a manifestation of the disease; in the treatment of disorders in which protein extravasation leads to the deposition of fibrin and extracellular matrix, promoting stromal proliferation (e.g. fibrosis, cirrhosis and carpals tunnel syndrome); ulcers including bacterial, fungal, Mooren ulcers and ulcerative colitis; or stromal deposition occurs in viral infections such as Herpes simplex, Herpes Zoster, AIDS, protozoan infections and toxoplasmosis, following trauma, radiation, stroke, endometriosis, ovarian hyperstimulation syndrome, systemic lupus, sarcoidosis, synovitis, Crohn's disease, sickle cell anemia, Lyme disease, pemphigoid, Paget's disease, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic occlusive pulmonary disease, asthma, and inflammatory rheumatoid or rheumatic disease; in the reduction of sub-cutaneous fat and for the treatment of obesity; ocular conditions such as ocular and macular edema, glaucoma, ocular neovascular disease, scleritis, radial keratotomy, uvetitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser complications, conjunctivitis, Stargardt's disease and Eales disease in addition to retinopathy and macular degeneration; cardiovascular conditions (e.g. atherosclerosis, restenosis, arteriosclerosis, vascular occlusion and carotid obstructive disease); cancer related indications (e.g. Ewing's sarcoma), retinoblastoma, rhabdomyosarcomas, neuroblastoma, hematopoietic malignancies, including tumor- induced pleural or pericardial effusions, and malignant ascites).

ADVANTAGE - (I) have kinase inhibitory activity such as VEGFR/KDR inhibitory activity and minimizes deleterious effects of VEGF (vascular endothelial growth factor). (I) act as inhibitors of other protein kinases e.g. p38, EGFR, CDK-2, CDK-5, IKK, JNK3, thus effective in the treatment of diseases associated with other protein kinases. (I) shows improvements in disorder severity and the frequency of incidence over treatment of each agent by itself, and also avoids adverse side effects associated with alternative therapies. Therefore, treatment with (I) prolongs the survivability of the patient by inhibiting the rapidly-proliferating cell growth associated with the neoplasm or effect a regression of the neoplasm.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-H; B07-H; B14-A01; B14-A02; B14-A03; B14-A04; B14-C03; B14-C06; B14-C09; B14-D06; B14-E08; B14-E10C; B14-E12; B14-F01; B14-F02D1; B14-F02F2; B14-F03; B14-F07; B14-G01B; B14-G02A; B14-G02B; **B14-H01**; B14-K01; B14-L06; B14-N01; B14-N03; B14-N04; B14-N14; B14-N16; B14-N17; B14-S04

TECH UPTX: 20021209

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) involves treatment of a compound of formula (II) with a primary amine in the presence of base and an inert solvent followed by coupling with a primary or secondary substituted benzylamine.
LG and Xa = halo.
All other definitions are defined as above.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The method further involves administering (I) in a **combination** with antibiotic-type agent, alkylating agent, antimetabolite agent, hormonal agent, immunological agent, interferon-type agent or miscellaneous agent.

ABEX UPTX: 20021209

SPECIFIC COMPOUNDS - 67 Compounds are specifically claimed as (I) e.g. N-(3,3-dimethyl-1-(1-methyl-piperidin-4-yl)-2,3-dihydro-1H-indol-6-yl)-2-(4-fluoro-benzylamino)-nicontinamide (Ia).

ADMINISTRATION - For oral administrations, the dose is 1 - 2000 (preferably 1 - 500) mg or a daily dose of 0.01 - 500 (preferably 0.1 - 50) mg/kg body weight. Also a composition containing (I) is administered orally, mucosally, topically, rectally, pulmonarily (including by inhalation, spray), parenterally (including intravenously, intravascularly, intraperitoneally, subcutaneously, intramuscularly, intrasternally) or by infusion.

EXAMPLE - A solution of N-(3,3-dimethyl-1-(1-methyl-piperidin-4-yl)-2,3-dihydro-1H-indol-5-yl)-2-fluoro-nicotinamide (500 mg), 4-fluoro-benzylamine (240 microl) and sodium bicarbonate (359 mg) was dissolved in isopropanol (5 ml) and heated to 85degreesC overnight. After cooling to room temperature, the mixture was dried under nitrogen. The residue was worked-up to give N-(3,3-dimethyl-1-(1-methyl-piperidin-4-yl)-2,3-dihydro-1H-indol-6-yl)-2-(4-fluoro-benzylamino)-nicotinamide (Ia).
DEFINITIONS - Full Definitions:
A1 and A2 = C or N;
A = 5 - 6 membered heteroaryl;
X = -C(=Z)-N-(R5a)-R4-;
Z = O or S;
Y = -Rz-N(R5)-C(Ra)(Rb)-, -N(R5)(Rz)-, -N(R5)-Rd-, -N(R5)-Rd-Rz-, -N(R5)-S(=O)p-, -N(R5)-C(Rb)(Ra)-, -N(R5)-C(Rb)(Ra)-Rz-, -N(R5)-S((=O)p)-Rz-, -Rz-N(R5)-S((=O)p)- or -N=CH-;
p = 0 - 2;
Ra and Rb = H, halo, cyano, -NHR6 or 1-4C alkyl substituted by R1;
Ra+Rb = 3-6C cycloalkyl;
Rz = 2-6C alkylenyl (in which one of the CH2 group may be replaced by O or -NH- or one of the CH2 group is optionally substituted with at least one of halo, cyano, -NHR6 or 1-4C alkyl substituted by R1);
Rd = cycloalkyl;
R1 = at least one of cycloalkyl, phenylalkyl, heterocyclyl, heterocyclylalkyl, phenyl (all optionally substituted), lower alkyl, cyano, lower hydroxyalkyl, lower carboxyalkyl, nitro, lower alkenyl, lower alkynyl, lower aminoalkyl, lower alkyaminoalkyl, lower haloalkyl, oxo, H or T;

T = halo, -OR7, -SR7, -CO2R7, -COR7, -CON(R7)2, -N(R7)2, SO2N(R7)2, -NR7C(O)OR7, or NR7C(O)R7;
R2 = 6 - 10 membered aryl, 5 - 6 membered heterocyclyl, 9 - 14 membered bicyclic or tricyclic heterocyclyl (all optionally substituted by T1), cycloalkyl or cycloalkenyl;
T1 = cycloalkyl, heterocyclyl, phenyl (all optionally substituted), -NH(1-4C alkylenyl-R9), SO2R7, -NR7C(O)N(R7)2, halosulfonyl, cyano, alkylaminoalkoxy, alkylaminoalkoxyalkoxy, nitro, or lower alkyl, lower alkenyl or lower alkynyl (all three substituted by R1), T, or -SO2R7;
R3 = aryl optionally substituted by at least one cycloalkyl, heterocyclyl, phenyl (all optionally substituted), nitro, alkylaminoalkoxyalkoxy, cyano, alkylaminoalkoxy, G1, T or -SO2R7;
G1 = lower alkyl, lower alkenyl or lower alkynyl (all optionally substituted by R1);
R4 = 2-4C alkylenyl, 2-4C alkenylenyl, or 2-4C alkynylenyl (in which one of CH2 is optionally substituted by O or NH), (all optionally substituted by OH) or direct bond;
R5 and R5a = H, lower alkyl, optionally substituted phenyl or lower aralkyl;
R6 = H or 1-6C alkyl;
R7 = phenyl, heterocyclyl, 3-6C cycloalkyl, phenyl-(1-6C)alkyl, heterocyclyl-(1-6C)alkyl, 3-6C cycloalkyl(1-6C)alkyl (all optionally substituted), lower haloalkyl, alkylaminoalkyl, H or lower alkyl;
R9 = phenyl, 5 - 6 membered heterocyclyl, 3-6C cycloalkyl (all optionally substituted) or H.
A1 - A2 from part of ring A.
Provided that;
a) when A is pyridyl, X is -C(O)NH-, Y is -NH-CH2-, R1 is H and R3 is 3-(N-methylaminocarbonyl)phenyl, 4-hydroxyphenyl, 3-hydroxyphenyl or phenyl, then R2 is not 3-trifluoromethylphenyl;
b) when Y is -NHSO2- then R2 is not substituted with -SO2N(R7)2;
c) when A is pyridyl, X is -C(O)NH-, Y is -N(benzyl)-CH2-, R1 is H and R3 is phenyl then R2 is not 3-trifluoromethylphenyl;
d) when A is pyridyl, X is -C(O)NH-, Y is -NH-CH2-, R1 is H and R3 is 2-methoxyphenyl or 3-methoxyphenyl, then R2 is not cyclohexyl,
d) when A is pyridyl, X is -C(O)NH-, X is -NH-CH2-, R1 is H and R3 is 2-methoxyphenyl or 3-methoxyphenyl, then R2 is not cyclohexyl,
e) when A is pyridyl then R1 is not 2-hydroxymethylpyrrol-5-yl;
f) when A is thienyl, then R1 is not 4-(methoxyaminocarbonylamino)phenyl;
g) when A is pyrimidyl, X is -C(O)NH- and Y is -NH-CH2- then R1 is not 2-pyridylmethoxy;
h) when A is pyrimidyl, X is -C(O)NH-, Y is -NH-CH2- and R3 is 3-chloro-4-methoxyphenyl then R1 is not 4-methylpiperidyl,
i) when A is pyrimidyl, X is C(O)NH-CH2-, Y is -NH-CH2- and R3 is 3-chloro-4-methoxyphenyl then R1 is not bromo,
j) when A is pyridyl then R2 is not 2-chloro-3-pyridyl; and
k) when A is pyridyl, X is C(O)NH-, Y is -NH-CH2-, R1 is H and R3 is phenyl, then R2 is not 2-methoxyphenyl.
Preferred Definitions:
A = pyridyl;
R1 = H, chloro or fluoro;
R2 = phenyl, tetrahydronaphthyl, indanyl, naphthyl, imidazolyl, oxazolyl, furyl, pyrrolyl, isoxazolyl, pyrazolyl, thiazolyl, thiadiazolyl, thienyl, pyridyl, pyrimidinyl, pyridazinyl, cyclohexyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3-dihydro-1H-indolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo(3,4-a)isoquinolyl, 3,4-dihydro-2H-benzo(1,4)oxazinyl or benzo(1,4)dioxanyl (all optionally substituted by halo, nitro, amino, cyano, aminoethyl, Boc-aminoethyl, hydroxy, aminosulfonyl, 4-methylpiperazinylsulfonyl, cyclohexyl, phenyl,

phenylmethyl, morpholinylmethyl, methylpiperazinylmethyl, morpholinylethyl, methylpiperazinylpropyl, 1-(4-morpholinyl)-2,2-dimethylpropyl, piperidinylmethyl, morpholinylpropyl, methylpiperidinylmethyl, piperidinylethyl, piperidinylpropyl, pyrrolidinylpropyl, pyrrolidinylpropenyl, pyrrolidinylbutenyl, fluorosulfonyl, methylsulfonyl, methylcarbonyl, piperidinylmethylcarbonyl, methylpiperazinylcarbonylethyl, methoxycarbonyl, 3-ethoxycarbonyl-2-methyl-fur-5-yl, methylpiperazinyl, methylpiperidyl, 1-methyl-(1,2,3,6-tetrahydropyridyl), imidazolyl, morpholinyl, 4-trifluoromethyl-1-piperidinyl, hydroxybutyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, sec-butyl, trifluoromethyl, pentafluoroethyl, nonafluorobutyl, dimethylaminopropyl, 1,1-di(trifluoromethyl)-1-hydroxymethyl, trifluoromethoxy, 1,1-di(trifluoromethyl)-1-(piperidinylethoxy)methyl, 1,1-di(trifluoromethyl)-1-(methoxyethoxyethoxy)methyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-aminoethyl, 2-aminoethyl, 1-(N-isopropylamino)ethyl, 2-(N-isopropylamino)ethyl, dimethylaminoethoxy, 4-chlorophenoxy, phenyloxy, 1-methylpiperidin-4-yloxy, isopropoxy, methoxy or ethoxy;
R3 = phenyl substituted by piperazinyl, morpholinyl, piperazinyl, phenyl (all optionally substituted), methyl, ethyl, propyl, cyano, hydroxymethyl, aminomethyl, NO2, trifluoromethyl, chloro, fluoro, bromo, hydroxy, methoxy, ethoxy, amino, dimethylamine, diethylamino, 1-methylpiperidinylmethoxy, aminosulfonyl, cyclohexyl, dimethylaminopropyl, dimethylaminoethoxy, 3-(4-morpholinyl)propyn-1-yl, or dimethylaminoethoxyethoxy.

L181 ANSWER 39 OF 40 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-265878 [27] WPIX
DOC. NO. CPI: C2001-080437
TITLE: New bicyclic heterocycle derivatives are androgen receptor agonists, partial agonists and antagonists, useful as contraceptives, for hormone replacement therapy, and for treating e.g. dysmenorrhea.
DERWENT CLASS: B02
INVENTOR(S): FARMER, L; HAMANN, L; HIGUCHI, R; MARTINBOROUGH, E; MOTAMEDI, M; PIO, B; TEGLEY, C; VAN OEVEREN, C A; WEST, S; ZHI, L; ARJAN VAN OEVEREN, C; TEGLEY, C M; VAN ARJAN, O C; HAMANN, L G; VAN OERVEREN, C A
PATENT ASSIGNEE(S): (LIGA-N) LIGAND PHARM INC; (FARM-I) FARMER L; (HAMA-I) HAMANN L G; (HIGU-I) HIGUCHI R; (MART-I) MARTINBOROUGH E; (MOTA-I) MOTAMEDI M; (PIOB-I) PIO B; (TEGL-I) TEGLEY C; (VOER-I) VAN OERVEREN C A; (WEST-I) WEST S; (ZHIL-I) ZHI L
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2001016108	A2	20010308	(200127)*	EN	356	C07D215-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW						
AU 2000070819	A	20010326	(200137)			C07D215-00
EP 1212303	A2	20020612	(200239)	EN		C07D215-00
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI						
BR 2000013653	A	20020514	(200240)			C07D215-00
NO 2002000912	A	20020429	(200241)			C07D000-00

CZ 2002000709	A3	20020814	(200263)		C07D215-00
SK 2002000274	A3	20020910	(200274)		C07D215-00
KR 2002040791	A	20020530	(200276)		C07D215-48
JP 2003508387	W	20030304	(200319)	440	C07D209-34
CN 1382124	A	20021127	(200322)		C07D215-22
HU 2002004337	A2	20030328	(200333)		C07D215-22
US 6566372	B1	20030520	(200336)		A61K031-47
US 2003130505	A1	20030710	(200347)		A61K031-551
ZA 2002001053	A	20030827	(200362)	450	C07D000-00
MX 2002002027	A1	20030501	(200415)		C07D215-00

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001016108	A2	WO 2000-US23585	20000825
AU 2000070819	A	AU 2000-70819	20000825
EP 1212303	A2	EP 2000-959507	20000825
		WO 2000-US23585	20000825
BR 2000013653	A	BR 2000-13653	20000825
		WO 2000-US23585	20000825
NO 2002000912	A	WO 2000-US23585	20000825
		NO 2002-912	20020225
CZ 2002000709	A3	WO 2000-US23585	20000825
		CZ 2002-709	20000825
SK 2002000274	A3	WO 2000-US23585	20000825
		SK 2002-274	20000825
KR 2002040791	A	KR 2002-702495	20020226
JP 2003508387	W	WO 2000-US23585	20000825
		JP 2001-519677	20000825
CN 1382124	A	CN 2000-814750	20000825
HU 2002004337	A2	WO 2000-US23585	20000825
		HU 2002-4337	20000825
US 6566372	B1 Provisional	US 1999-150987P	19990827
		US 2000-649466	20000824
US 2003130505	A1 Provisional	US 1999-150987P	19990827
	Div ex	US 2000-649466	20000824
		US 2002-299909	20021118
ZA 2002001053	A	ZA 2002-1053	20020206
MX 2002002027	A1	WO 2000-US23585	20000825
		MX 2002-2027	20020226

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000070819	A Based on	WO 2001016108
EP 1212303	A2 Based on	WO 2001016108
BR 2000013653	A Based on	WO 2001016108
CZ 2002000709	A3 Based on	WO 2001016108
SK 2002000274	A3 Based on	WO 2001016108
JP 2003508387	W Based on	WO 2001016108
HU 2002004337	A2 Based on	WO 2001016108
MX 2002002027	A1 Based on	WO 2001016108

PRIORITY APPLN. INFO: US 1999-150987P 19990827; US 2000-649466 20000824; US 2002-299909 20021118

INT. PATENT CLASSIF.:
MAIN: A61K031-47; A61K031-551; C07D000-00; C07D209-34;

C07D215-00; C07D215-22; C07D215-48
SECONDARY: A61K031-366; A61K031-37; A61K031-404; A61K031-407; A61K031-428; A61K031-4704; A61K031-4706; A61K031-4709; A61K031-4725; **A61K031-496**; A61K031-517; A61K031-536; A61K031-5377; **A61K031-538**; A61K031-55; A61P005-24; A61P005-26; A61P005-28; A61P005-34; A61P005-36; A61P007-04; A61P007-06; A61P013-08; A61P015-00; A61P015-04; A61P015-08; A61P015-10; A61P015-16; A61P015-18; A61P017-10; A61P017-14; A61P035-00; A61P043-00; C07D209-96; C07D215-227; C07D215-36; C07D215-38; C07D239-80; C07D265-18; C07D265-36; C07D277-68; C07D311-08; C07D311-14; C07D401-04; C07D405-12; C07D409-12; C07D413-04

BASIC ABSTRACT:

WO 200116108 A UPAB: 20010518

NOVELTY - Bicyclic heteroaryl compounds (I)-(IX) and their salts are new.

DETAILED DESCRIPTION - Bicyclic heteroaryl compounds of formula (I)-(IX) and their salts are new.

R1, R2 = COR3, CSR3, SOOR3, NO, NR3R4, or 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, 1-8C haloalkyl, 2-8C (halo)alkenyl, 2-8C haloalkynyl, 1-8C heteroalkyl, 2-8C heteroalkenyl, 2-8C heteroalkynyl, (CH2)nR3a, aryl or heteroaryl (all optionally substituted by A1); or

R1 + R2 = 3-9 membered alkyl, alkenyl, heteroalkyl or heteroalkenyl ring (all optionally substituted by A2) or a heterocyclic group;

A1 = halo, OR3, NR3R4, CN, NO2, SR3, SOR3, SOOR3, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl;

A2 = halo, OR3, NR3R4, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl);

R3, R4 = H, or 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, 1-8C haloalkyl, 1-8C heteroalkyl (all optionally substituted by halo, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl);

R3a = aryl or heteroaryl (optionally substituted by halo, CN, NO2, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl;

R5 = H, halo, OR3, NR3R4, SR3, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl);

R6 = halo, Me, CF3, CHF2, CH2F, CN, CF2Cl, CF2OR3, OR3, SR3, SOR3, SOOR3, COOR3, NR3R4, or 1-4C alkyl, 2-4C alkenyl, 2-4C alkynyl, 1-4C haloalkyl, 2-4C haloalkenyl, 2-4C haloalkynyl, 1-4C heteroalkyl, 2-4C heteroalkenyl or 2-4C heteroalkynyl (all optionally substituted by F, Cl, Br, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl);

R7, R8 = H, halo, CN, OR3, NR3R4, NR3CR3R4CONR3R4, Cn(R3)2nOR3, SR3, SOR3, SOOR3, NR3COR4, 1-8C alkyl, 1-8C haloalkyl or 1-8C heteroalkyl;

R9 = H, halo, OR3, NR3R4, SR3, SOR3, SOOR3, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl;

R10 = NR2R1 or a heterocyclic group;

R11 = halo, 1-6C alkyl, 1-6C haloalkyl, 1-6C heteroalkyl, NO2, CN, CF3, OR3, NR3R4, SR3, SOR3, or SOOR3;

R12 = halo, 1-4C haloalkyl, CN, CF3, OR3, NR3R4, SR3, SOR3, or SOOR3;

R13 = halo, CN, CF3, OR3, NR3R4, SR3, SOR3, SOOR3, COR3, COOR3, 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, 1-8C haloalkyl, 2-8C haloalkenyl, 2-8C haloalkynyl, 1-8C heteroalkyl, 2-8C heteroalkenyl, 2-8C heteroalkynyl (all optionally substituted by A3) or (CH2)nR3a;

A3 = halo, OR3, NR3R4, CN, NO2, SR3, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl;

R13a = NHR1, or heteroaryl (optionally substituted by A3);

R14 = halo, CF3, CHF2, CHF2, CF2Cl, or CF2OR3;

R15 = halo, CN, OR16, NR16R4, CR16, CH2R16, COR3, COOR3, CONR3R4, SOR3, SOOR3, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl;

R16 = H, 1-8C alkyl, 1-8C haloalkyl, 1-8C heteroalkyl, CH2R3a, aryl,

heteroaryl, COR17, COOR17 or CON(R17)2;
R17 = H, 1-4C alkyl, 1-4C haloalkyl, or 1-4C heteroalkyl;
R18, R19 = H, 1-6C alkyl, 1-6C haloalkyl or 1-6C heteroalkyl; or
R18 + R19 = 3-7 membered ring;
R20 = aryl or heteroaryl (both optionally substituted by F, Cl, Br, CN, OR3, SR3, SOR3, SOOR3, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl);
R21 = CR3R4CONR3R4, Cn(R3)2nOR3, SOR3, SOOR3, 2-8C alkyl, 2-8C haloalkyl or 2-8C heteroalkyl;
R22, R23 = H, 1-6C alkyl, 1-6C haloalkyl or 1-6C heteroalkyl; or
R22 + R23 = 3-7 membered ring;
R24 = H or OR3;
R25 - R30 = H, halo, OR3, NR3R4, SR3, SOR3, SOOR3, or 1-6C alkyl, 1-6C haloalkyl, 1-6C heteroalkyl, 2-6C alkenyl or 2-6C alkynyl (all optionally substituted by halo, OR3, NR3R4, 1-4C alkyl, 1-4C haloalkyl, 1-4C heteroalkyl or aryl or heteroaryl (both optionally substituted by halo, CN, NO2, OH, OMe, CF3 or 1-6C alkyl)); or
2 of R25 - R30 = 3-7 membered alkyl, alkenyl or heteroalkyl ring; or
4 of R25 - R30 = fused aromatic ring;
Q = O or S;
U = V, OCR22R23, SCR22R23, NR3CR22R23 or CR3R4CR22R23;
V = O, NR3, CR22R23, CR3R4O or CR3R4S;
W = O, S, NR3 or CR3R4;
X = O, S or NR16;
Y = O, S, NR3, CR3R4 or NOR3;
Z = O, S, NR3, C=O, 2H or CR25R26;
n = 1-3; and
m = 1-5.

An INDEPENDENT CLAIM is also included for a pharmaceutical composition comprising a compound of formula (X) - (XIII) and a carrier.

M = O, S or NR16;

R31 = H, halo CN, OR1, NHR1, COR3, COOR3, SR1, SOR1, SOOR1, or 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, 1-8C haloalkyl, 2-8C haloalkenyl, 2-8C haloalkynyl, 1-8C heteroalkyl, 2-8C heteroalkenyl, 2-8C heteroalkynyl, (CH2)nR3 or heteroaryl (all optionally substituted by halo, CN, OR1, NR1R3, SR1, SOR3, SOOR3, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl), NR1R3, phenyl substituted by (R11)m, or a heterocyclic group of formula (iii)-(vi); and

R42 = H, halo, Me, CF3, CHF2, CH2F, CN, CF2Cl, CF2OR3, OR3, SR3, SOR3, SOOR3, NR3R4, or 1-4C alkyl, 1-4C haloalkyl, 1-4C heteroalkyl, 2-4C alkenyl, 2-4C alkynyl, 2-4C haloalkenyl, 2-4C haloalkynyl, 2-4C heteroalkenyl or 2-4C heteroalkynyl (all optionally substituted by halo, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl).

ACTIVITY - Cytostatic; gynecological; contraceptive; abortifacient; anabolic; analgesic; immunomodulator; antiacne; dermatological; antidepressant; depilatory.

In an androgen receptor (AR) binding assay using CV-1 cells, 6-propylamino-4-trifluoromethyl-2(1H)-quinoline (IVa) had a Ki of 54 nM, 34% and 74% efficacy as an AR agonist and antagonist respectively, and a potency of 2022 and 27 nM as an AR agonist and antagonist respectively.

MECHANISM OF ACTION - Androgen receptor modulator; androgen receptor agonist; androgen receptor antagonist; androgen receptor partial agonist; progesterone receptor modulator; progesterone receptor agonist; progesterone receptor antagonist; progesterone receptor partial agonist;

USE - The compounds can be used to treat hypogonadism, wasting diseases, cancer cachexia, hirsutism, stimulation of hematopoiesis, acne, male pattern baldness, prostatic hyperplasia, hormone dependent cancers e.g. prostate, ovarian, endometrial and breast cancers, uterine bleeding, dysmenorrhea, endometriosis, leiomyomas, hot flushes, mood disorders, meningiomas, and for male contraception, hormone replacement therapy,

female fertility modulators e.g. contraceptives, contragestational agents and abortifacients.
Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-H; B14-D01; B14-E11; **B14-H01**; B14-J01A4; B14-J01B3; B14-N14; B14-N17; B14-P01A; B14-R02
TECH UPTX: 20010518
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Quinolinone compounds are prepared by e.g. Knorr cyclization of a substituted aniline with a ketone, and optionally further derivatizing functional groups.
ABEX UPTX: 20010518
SPECIFIC COMPOUNDS - 361 Compounds (I)-(IX) are specifically claimed e.g. 6-propylamino-4-trifluoromethyl-2(1H)-quinoline (IVa).

ADMINISTRATION - Administration is 1 microg/kg/dose-500 mg/kg/dose, preferably 20 microg/kg/dose-20 mg/kg/dose e.g. orally, topically, rectally or parenterally.

EXAMPLE - To a solution of 6-amino-4-trifluoromethyl-2(1H)-quinolinone (35 mg) in MeOH (20 ml) was added propionaldehyde (2-5 equivalents) and NaCNBH3 (2-5 equivalents). The mixture was stirred at room temperature for 4 hours and water (20 ml) was added. The aqueous layer was extracted with ethyl acetate (2 x 20 ml) and the **combined** organic layers were washed with brine and dried over MgSO4. Concentration and purification by flash chromatography gave 6-propylamino-4-trifluoromethyl-2(1H)-quinoline (IVa) as a yellow solid.
DEFINITIONS - Full definitions: Compounds (I)-(IX).
R1, R2 = COR3, CSR3, SOOR3, NO, NR3R4, or 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, 1-8C haloalkyl, 2-8C (halo)alkenyl, 2-8C haloalkynyl, 1-8C heteroalkyl, 2-8C heteroalkenyl, 2-8C heteroalkynyl, (CH2)nR3a, aryl or heteroaryl (all optionally substituted by A1); or
R1 + R2 = 3-9 membered alkyl, alkenyl, heteroalkyl or heteroalkenyl ring (all optionally substituted by A2) or a group of formula (i) or (ii);
A1 = halo, OR3, NR3R4, CN, NO2, SR3, SOR3, SOOR3, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl;
A2 = halo, OR3, NR3R4, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl);
R3, R4 = H, or 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, 1-8C haloalkyl, 1-8C heteroalkyl (all optionally substituted by halo, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl);
R3a = aryl or heteroaryl (optionally substituted by halo, CN, NO2, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl;
R5 = H, halo, OR3, NR3R4, SR3, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl);
R6 = halo, Me, CF3, CHF2, CH2F, CN, CF2Cl, CF2OR3, OR3, SR3, SOR3, SOOR3, COOR3, NR3R4, or 1-4C alkyl, 2-4C alkenyl, 2-4C alkynyl, 1-4C haloalkyl, 2-4C haloalkenyl, 2-4C haloalkynyl, 1-4C heteroalkyl, 2-4C heteroalkenyl or 2-4C heteroalkynyl (all optionally substituted by F, Cl, Br, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl);
R7, R8 = H, halo, CN, OR3, NR3R4, NR3CR3R4CONR3R4, Cn(R3)2nOR3, SR3, SOR3, SOOR3, NR3COR4, 1-8C alkyl, 1-8C haloalkyl or 1-8C heteroalkyl;
R9 = H, halo, OR3, NR3R4, SR3, SOR3, SOOR3, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl;
R10 = NR2R1 or a group of formula (iii)-(vi);
R11 = halo, 1-6C alkyl, 1-6C haloalkyl, 1-6C heteroalkyl, NO2, CN, CF3, OR3, NR3R4, SR3, SOR3, or SOOR3;
R12 = halo, 1-4C haloalkyl, CN, CF3, OR3, NR3R4, SR3, SOR3, or SOOR3;
R13 = halo, CN, CF3, OR3, NR3R4, SR3, SOR3, SOOR3, COR3, COOR3, 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, 1-8C haloalkyl, 2-8C haloalkenyl, 2-8C

haloalkynyl, 1-8C heteroalkyl, 2-8C heteroalkenyl, 2-8C heteroalkynyl (all optionally substituted by A3) or (CH2)nR3a;
A3 = halo, OR3, NR3R4, CN, NO2, SR3, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl;
R13a = NHR1, or heteroaryl (optionally substituted by A3);
R14 = halo, CF3, CHF2, CHF2, CF2Cl, or CF2OR3;
R15 = halo, CN, OR16, NR16R4, CR16, CH2R16, COR3, COOR3, CONR3R4, SOR3, SOOR3, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl;
R16 = H, 1-8C alkyl, 1-8C haloalkyl, 1-8C heteroalkyl, CH2R3a, aryl, heteroaryl, COR17, COOR17 or CON(R17)2;
R17 = H, 1-4C alkyl, 1-4C haloalkyl, or 1-4C heteroalkyl;
R18, R19 = H, 1-6C alkyl, 1-6C haloalkyl or 1-6C heteroalkyl; or
R18 + R19 = 3-7 membered ring;
R20 = aryl or heteroaryl (both optionally substituted by F, Cl, Br, CN, OR3, SR3, SOR3, SOOR3, 1-4C alkyl, 1-4C haloalkyl or 1-4C heteroalkyl);
R21 = CR3R4CONR3R4, Cn(R3)2nOR3, SOR3, SOOR3, 2-8C alkyl, 2-8C haloalkyl or 2-8C heteroalkyl;
R22, R23 = H, 1-6C alkyl, 1-6C haloalkyl or 1-6C heteroalkyl; or
R22 + R23 = 3-7 membered ring;
R24 = H or OR3;
R25 - R30 = H, halo, OR3, NR3R4, SR3, SOR3, SOOR3, or 1-6C alkyl, 1-6C haloalkyl, 1-6C heteroalkyl, 2-6C alkenyl or 2-6C alkynyl (all optionally substituted by halo, OR3, NR3R4, 1-4C alkyl, 1-4C haloalkyl, 1-4C heteroalkyl or aryl or heteroaryl (both optionally substituted by halo, CN, NO2, OH, OMe, CF3 or 1-6C alkyl)); or
2 of R25 - R30 = 3-7 membered alkyl, alkenyl or heteroalkyl ring; or
4 of R25 - R30 = fused aromatic ring;
Q = O or S;
U = V, OCR22R23, SCR22R23, NR3CR22R23 or CR3R4CR22R23;
V = O, NR3, CR22R23, CR3R4O or CR3R4S;
W = O, S, NR3 or CR3R4;
X = O, S or NR16;
Y = O, S, NR3, CR3R4 or NOR3;
Z = O, S, NR3, C=O, 2H or CR25R26;
n = 1-3; and
m = 1-5.

L181 ANSWER 40 OF 40 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-322267 [28] WPIX
CROSS REFERENCE: 2002-519656 [55]
DOC. NO. CPI: C1998-099043
TITLE: Aralkyl and aralkylidene heterocyclic lactam and imide derivatives - to treat hypertension, depression, anxiety, sexual dysfunction, eating disorders, chemical dependency, migraine, Alzheimer's disease and Parkinson's disease.
DERWENT CLASS: B02 B03
INVENTOR(S): HOWARD, H R; CHAPPELL, P B; GIBBS, M A; SCHACHTER, J B; SPROUSE, J S
PATENT ASSIGNEE(S): (PFIZ) PFIZER INC; (CHAP-I) CHAPPELL P B; (GIBB-I) GIBBS M A; (HOWA-I) HOWARD H R; (SCHA-I) SCHACHTER J B; (SPRO-I) SPROUSE J S
COUNTRY COUNT: 80
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 9814433	A1	19980409	(199828)*	EN	90	C07D233-96

RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX
NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU

AU 9739514	A	19980424	(199835)			
ZA 9708703	A	19990526	(199927)		90	C07D000-00
NO 9901525	A	19990528	(199931)			C07D233-96
EP 929528	A1	19990721	(199933)	EN		

R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV NL PT RO SE SI

CN 1231661	A	19991013	(200008)			C07D233-96
HU 9903443	A2	20000128	(200015)			
JP 2000503679	W	20000328	(200026)		101	C07D233-96
BR 9713239	A	20000404	(200030)			
CZ 9901071	A3	20000517	(200031)			C07D233-96
SK 9900410	A3	20000912	(200055)			C07D233-96
NZ 334215	A	20000929	(200060)			A61K031-425
MX 9903047	A1	19990801	(200063)			C07D233-96
JP 3121355	B2	20001225	(200102)		45	C07D233-96
KR 2000048731	A	20000725	(200116)			C07D233-96
AU 732451	B	20010426	(200128)			C07D233-96
CN 1329002	A	20020102	(200227)			C07D401-06
US 2002049214	A1	20020425	(200233)			C07D403-02
US 6380186	B1	20020430	(200235)			A61K031-538<--
US 2002072519	A1	20020613	(200243)			A61K031-55
US 6403592	B1	20020611	(200244)			A61K031-451
US 2002091117	A1	20020711	(200248)			A61K031-55
US 2002091118	A1	20020711	(200248)			A61K031-55
US 2002091119	A1	20020711	(200248)			A61K031-55
US 6423708	B1	20020723	(200254)			A61K031-538<--
KR 323167	B	20020204	(200255)			C07D233-96
NO 313192	B1	20020826	(200263)			C07D233-96
US 2002147194	A1	20021010	(200269)			A61K031-54
US 6472388	B2	20021029	(200274)			A61K031-5377
CA 2266107	C	20021203	(200306)	EN		C07D233-96
KR 346620	B	20020726	(200309)			C07D403-14
TW 491842	A	20020621	(200323)			C07D233-96
US 6562813	B2	20030513	(200335)			A61K031-541
EP 929528	B1	20030723	(200356)	EN		C07D233-96

R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV NL PT RO SE SI

DE 69723711	E	20030828	(200364)			C07D233-96
US 6627627	B2	20030930	(200367)			A61K031-541
ES 2202634	T3	20040401	(200425)			C07D233-96
MX 217026	B	20031020	(200467)			A61K031-415

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9814433	A1	WO 1997-IB1062	19970908
AU 9739514	A	AU 1997-39514	19970908
ZA 9708703	A	ZA 1997-8703	19970929
NO 9901525	A	WO 1997-IB1062	19970908
		NO 1999-1525	19990329
EP 929528	A1	EP 1997-936823	19970908
		WO 1997-IB1062	19970908
CN 1231661	A	CN 1997-198344	19970908
HU 9903443	A2	WO 1997-IB1062	19970908
		HU 1999-3443	19970908
JP 2000503679	W	WO 1997-IB1062	19970908
		JP 1998-516337	19970908
BR 9713239	A	BR 1997-13239	19970908

			WO 1997-IB1062	19970908
CZ 9901071	A3		WO 1997-IB1062	19970908
			CZ 1999-1071	19970908
SK 9900410	A3		WO 1997-IB1062	19970908
			SK 1999-410	19970908
NZ 334215	A		NZ 1997-334215	19970908
			WO 1997-IB1062	19970908
MX 9903047	A1		MX 1999-3047	19990330
JP 3121355	B2		WO 1997-IB1062	19970908
			JP 1998-516337	19970908
KR 2000048731	A		WO 1997-IB1062	19970908
			KR 1999-702707	19990329
AU 732451	B		AU 1997-39514	19970908
CN 1329002	A		CN 2001-118954	19970908
US 2002049214	A1	Provisional	US 1996-27111P	19960930
		CIP of	WO 1997-IB1062	19970908
		CIP of	US 1999-254999	19991008
			US 2000-733346	20001208
US 6380186	B1	Provisional	US 1996-27111P	19960930
			WO 1997-IB1062	19970908
			US 1999-254999	19991008
US 2002072519	A1	Provisional	US 1996-27111P	19960930
		Cont of	WO 1997-IB1062	19970908
		Cont of	US 1999-254999	19991008
			US 2001-993741	20011106
US 6403592	B1	Provisional	US 1996-27111P	19960930
		Div ex	WO 1997-IB1062	19970908
		Div ex	US 1999-254999	19991008
			US 2001-11505	20011106
US 2002091117	A1	Provisional	US 1996-27111P	19960930
		Div ex	WO 1997-IB1062	19970908
		Div ex	US 1999-254999	19991008
			US 2001-994027	20011106
US 2002091118	A1	Provisional	US 1996-27111P	19960930
		Div ex	WO 1997-IB1062	19970908
		Div ex	US 1999-254999	19991008
			US 2001-11505	20011106
US 2002091119	A1	Provisional	US 1996-27111P	19960930
		Div ex	WO 1997-IB1062	19970908
		Div ex	US 1999-254999	19991008
			US 2001-11568	20011106
US 6423708	B1	Provisional	US 1996-27111P	19960930
		CIP of	WO 1997-IB1062	19970908
		CIP of	US 1999-254999	19991008
			US 2000-733346	20001208
KR 323167	B		WO 1997-IB1062	19970908
			KR 1999-702707	19990329
NO 313192	B1		WO 1997-IB1062	19970908
			NO 1999-1525	19990329
US 2002147194	A1	Provisional	US 1996-27111P	19960930
		Cont of	WO 1997-IB1062	19970908
		Cont of	US 1999-254999	19991008
			US 2002-91963	20020306
US 6472388	B2	Provisional	US 1996-27111P	19960930
		Div ex	WO 1997-IB1062	19970908
		Div ex	US 1999-254999	19991008
			US 2001-994027	20011106
CA 2266107	C		CA 1997-2266107	19970908
			WO 1997-IB1062	19970908
KR 346620	B		WO 1997-IB1062	19970908

		Div ex	KR 1999-702707	19990329
			KR 2001-705172	20010425
TW 491842	A		TW 1997-114090	19970926
US 6562813	B2	Provisional	US 1996-27111P	19960930
		Cont of	WO 1997-IB1062	19970908
		Cont of	US 1999-254999	19991008
			US 2002-91963	20020306
EP 929528	B1		EP 1997-936823	19970908
			WO 1997-IB1062	19970908
DE 69723711	E		DE 1997-623711	19970908
			EP 1997-936823	19970908
			WO 1997-IB1062	19970908
US 6627627	B2	Provisional	US 1996-27111P	19960930
		Cont of	WO 1997-IB1062	19970908
		Cont of	US 1999-254999	19991008
			US 2001-993741	20011106
ES 2202634	T3		EP 1997-936823	19970908
MX 217026	B		WO 1997-IB1062	19970908
			MX 1999-3047	19990330

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9739514	A	Based on	WO 9814433
EP 929528	A1	Based on	WO 9814433
HU 9903443	A2	Based on	WO 9814433
JP 2000503679	W	Based on	WO 9814433
BR 9713239	A	Based on	WO 9814433
CZ 9901071	A3	Based on	WO 9814433
NZ 334215	A	Based on	WO 9814433
JP 3121355	B2	Previous Publ.	JP 200003679
		Based on	WO 9814433
KR 2000048731	A	Based on	WO 9814433
AU 732451	B	Previous Publ.	AU 9739514
		Based on	WO 9814433
US 6380186	B1	Based on	WO 9814433
KR 323167	B	Previous Publ.	KR 2000048731
		Based on	WO 9814433
NO 313192	B1	Previous Publ.	NO 9901525
US 2002147194	A1	Cont of	US 6380186
CA 2266107	C	Based on	WO 9814433
KR 346620	B	Based on	WO 9814433
US 6562813	B2	Cont of	US 6380186
EP 929528	B1	Based on	WO 9814433
DE 69723711	E	Based on	EP 929528
		Based on	WO 9814433
US 6627627	B2	Cont of	US 6380186
ES 2202634	T3	Based on	EP 929528
MX 217026	B	Based on	WO 9814433

PRIORITY APPLN. INFO: US 1996-27111P 19960930; US
1999-254999 19991008; US
2000-733346 20001208; US
2001-993741 20011106; US
2001-11505 20011106; US
2001-994027 20011106; US
2001-11568 20011106; US
2002-91963 20020306

INT. PATENT CLASSIF.:

MAIN: A61K031-415; A61K031-425; A61K031-451; A61K031-5377; **A61K031-538**; A61K031-54; A61K031-541; A61K031-55; C07D000-00; C07D233-96; C07D401-06; C07D403-02; C07D403-14

SECONDARY: A61K031-40; A61K031-4015; A61K031-4166; A61K031-4178; A61K031-426; A61K031-4439; A61K031-445; **A61K031-496**; A61K031-497; A61K031-535; A61K031-5355; A61K031-5415; A61P025-06; A61P025-24; A61P043-00; C07B000-00; C07C255-01; C07D207-12; C07D207-24; C07D207-26; C07D207-36; C07D211-40; C07D211-52; C07D223-10; C07D233-76; C07D233-78; C07D265-32; C07D277-20; C07D277-34; C07D279-12; C07D295-04; C07D295-06; C07D295-073; C07D401-02; C07D403-06; C07D413-08; C07D417-08; C07D417-10

BASIC ABSTRACT:

WO 9814433 A UPAB: 20041019

Aralkyl and aralkylidene heterocyclic lactam and imide derivatives of formula (I), and their salts, are new: R1 = G1-G7; a = 0-8; R13 = 1-4C alkyl or a 1-4C methylene bridge from one of the C atoms of the piperazine or piperidine ring of G1 or G2 to the same or another ring C or ring N of the piperazine or piperidine ring of G1 or G2, having a bonding site, or to a ring C of R6 having a bonding site; E = O, S, SO or SO2; X = H, Cl, F, Br, I, CN, 1-6C alkyl, OH, CF3, 1-6C alkoxy, SOt(1-6C alkyl) (where t = 0-2), COOR10 or CONR11R12; Y = optionally substituted 1-4C heteroalkyl bridge that, together with the atoms to which it is attached, forms a 5-7 membered heterocycle containing 2-4 heteroatoms selected from 1,3-oxazolidin-4-on-5-yl, 1,3-oxazolidin-2,4-dion-5-yl, 4,5-dihydro-1,2-oxazolidin-3-on-4-yl, 1,3-thiazolidin-4-on-5-yl, 1,3-thiazolidin-2,4-dion-5-yl, 1,3-pyrazolidin-4-on-5-yl, 1,3-imidazolidin-2,4-dion-5-yl, 1,2-pyrazolidin-3-on-4-yl, 1,2-thiazolidin-1,1,3-trion-4-yl, 1,2-thiazolidin-3-on-4-yl, tetrahydro-1,2-oxazin-3-on-4-yl, tetrahydro-1,3-oxazin-4-on-5-yl, tetrahydro-1,3-oxazin-2,4-dion-5-yl, morpholin-3-on-2-yl, morpholin-3,5-dion-2-yl, 2,3-dihydro-1,4-oxazin-3-on-2-yl, tetrahydro-1,3-thiazin-4-on-5-yl, tetrahydro-1,3-thiazin-2,4-dion-5-yl, tetrahydro-1,2-thiazin-3-on-4-yl, thiomorpholin-3-on-2-yl, thiomorpholin-3,5-dion-2-yl, 2,3-dihydro-1,4-thiazin-3-on-2-yl, hexahydro-1,2-diazin-3-on-4-yl, 4,5-dihydro-2H-pyridazin-3-on-4-yl, hexahydro-1,3-diazin-4-on-5-yl, hexahydro-1,3-diazin-2,4-dion-5-yl, piperazin-2-on-3-yl, piperazin-2,6-dion-3-yl, tetrahydro-1,3,4-thiadiazin-5-on-6-yl, 5,6-dihydro-1,3,4-thiadiazin-5-on-6-yl, 1,3,4-oxadiazin-5-on-6-yl, 5,6-dihydro-1,2,4-oxadiazin-5-on-6-yl, tetrahydro-1,2,4-oxadiazin-5-on-6-yl, 1,2,4-triazin-5-on-6-yl, tetrahydro-1,2,4-oxadiazin-5-on-6-yl, 5,6-dihydro-1,2,4-oxadiazin-5-on-6-yl, 1,2,4-oxadiazin-3,5-dion-6-yl, 1,2,4-triazin-6-on-5-yl, hexahydro-1,2-oxazepin-3-on-2-yl, hexahydro-1,3-oxazepin-4-on-5-yl, hexahydro-1,4-oxazepin-3-on-2-yl, hexahydro-1,4-oxazepin-3,5-dion-2-yl, hexahydro-1,4-oxazepin-3,5-dion-6-yl, 2,3,5,6-tetrahydro-1,4-oxazepin-5,7-dion-6-yl, hexahydro-1,4-oxazepin-5-on-6-yl, hexahydro-1,3-oxazepin-2,4-dion-5-yl, hexahydro-1,2-thiazepin-3-on-4-yl, hexahydro-1,4-thiazepin-3-on-2-yl, 2,3,4,5-tetrahydro-1,4-thiazepin-3-on-2-yl, hexahydro-1,4-thiazepin-3,5-dion-2-yl, hexahydro-1,4-thiazepin-3,5-dion-6-yl, 2,3,6,7-tetrahydro-1,4-thiazepin-5-on-6-yl, 6,7-dihydro-1,4-thiazepin-5-on-6-yl, hexahydro-1,3-thiazepin-2,4-dion-5-yl, hexahydro-1,2-diazepin-3-on-4-yl, hexahydro-1,3-diazepin-2,4-dion-5-yl, hexahydro-1,4-diazepin-2-on-3-yl, hexahydro-1,4-diazepin-5-on-6-yl, hexahydro-1,4-diazepin-5,7-dion-6-yl, hexahydro-1,3,5-thiadiazepin-3-on-7-yl, 4,5,6,7-tetrahydro-1,3,5-thiadiazepin-6-on-7-yl, 2,3,5,6-tetrahydro-1,2,4-triazepin-3,5-dion-7-yl; where the substituents on any of the C atoms capable of supporting an additional bond, of the heteroalkyl bridge, are Cl, F, 1-6C alkyl, 1-6C alkoxy, CF3 or CN; where

the substituents on any of the N atoms capable of supporting an additional bond, of the heteroalkyl bridge, are 1-6C alkyl or CF3; R2 = H, 1-4C alkyl, Ph or naphthyl (Ph or naphthyl being optionally substituted by F, Cl, Br, I, 1-6C alkyl, 1-6C alkoxy, CF3, CN or SOk(1-6C alkyl); k = 0-2; R3 = (CH2)mB; m = 0-3; B = H; or is Ph, naphthyl or a 5-6 membered heteroaryl group containing 1-4 heteroatoms in the ring (all optionally substituted by F, Cl, Br, I, 1-6C alkyl, 1-6C alkoxy, (1-6C alkoxy)-(1-6C alkyl), CF3, OCF3, CN, OH, COOH or SOn(1-6C alkyl); n = 0-2; R6 = H, 1-6C alkyl optionally substituted by 1-6C alkoxy or 1-3 F atoms, or (1-4C alkyl)aryl where the aryl moiety = Ph, naphthyl or heteroaryl-(CH2)q, where the heteroaryl moiety is selected from pyridyl, pyrimidyl, benzoxazolyl, benzothiazolyl, benzisoxazolyl and benzisothiazolyl; and where the aryl and heteroaryl moieties may be substituted by one or more of F, Cl, Br, I, 1-6C alkyl, 1-6C alkoxy, CF3, CN and SOg(1-6C alkyl); g = 0-2; q = 0-4; R7 = H, 1-6C alkyl, (1-4C alkyl)aryl where the aryl moiety is Ph, naphthyl or heteroaryl-(CH2)r, where the heteroaryl moiety is selected from pyridyl, pyrimidyl, benzoxazolyl, benzothiazolyl, benzisoxazolyl and benzisothiazolyl; and where the aryl and heteroaryl moieties may be substituted by F, Cl, Br, I, 1-6C alkyl, 1-6C alkoxy, CF3, C(=O)(1-6C alkyl), CN or SOj(1-6C alkyl); r = 0-4; j = 0-2; or R6+R7 = a 2-4C chain; R8 = H or 1-3C alkyl; R9 = H or 1-6C alkyl; or NR6R9 = 5-7 membered heteroalkyl ring containing 0-4 heteroatoms selected from N, S and O; p = 1-3; R10, R11, R12 = as for R2; or NR11R12 = a 5-7 membered heteroalkyl ring containing 0-4 heteroatoms selected from N, S and O; and the dashed lines = optional bonds; provided that when the dashed line in G2 gives a double bond, R8 is absent.

Also claimed are compounds of formula (V).

USE - Claimed use of (I) is to treat hypertension, depression, generalised anxiety disorder, phobias, post-traumatic stress syndrome, avoidant personality disorder, sexual dysfunction (particularly premature ejaculation), eating disorders, obesity, chemical dependencies, cluster headache, migraine, pain, Alzheimer's disease, obsessive-compulsive disorder, panic disorder, memory disorders, Parkinson's disease, endocrine disorders, vasospasm, cerebellar ataxia, gastrointestinal tract disorders, negative symptoms of schizophrenia, premenstrual syndrome, Fibromyalgia Syndrome, stress incontinence, Tourette syndrome, trichotillomania, kleptomania, male impotence, cancer, chronic paroxysmal hemicrania and headache.

Use of (I) in **combination** with a 5-HT re-uptake inhibitor (preferably sertraline) is claimed.

Also claimed is treatment of a disorder that can be treated by enhancing serotonergic neurotransmission by administration of a 5-HT-1A antagonist in **combination** with a 5-HT-1D antagonist of formula (I).

(V) are useful as intermediates.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-H; B07-H; B14-C01; B14-E10; B14-E12; B14-F02B; **B14-H01**; B14-J01; B14-J01A1; B14-J01A3; B14-J01A4; B14-J01B4; B14-P02

=>

=> fil hcap

FILE 'HCAPLUS' ENTERED AT 15:07:46 ON 31 JAN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 31 Jan 2005 VOL 142 ISS 6
FILE LAST UPDATED: 30 Jan 2005 (20050130/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> fil medlin

FILE 'MEDLINE' ENTERED AT 15:07:49 ON 31 JAN 2005

FILE LAST UPDATED: 29 JAN 2005 (20050129/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

Warning: The search L-number/HUMAN limit is missing from records indexed
with the new 2005 MeSH (records added since December 19, 2004). Until
this is corrected, include HUMANS/CT and 20041219-20051231/ED in
searches to limit results to humans for this time period.

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2005 vocabulary. See http://www.nlm.nih.gov/mesh/ and
http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
description of changes.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> fil pascal

FILE 'PASCAL' ENTERED AT 15:07:52 ON 31 JAN 2005

FILE LAST UPDATED: 31 JAN 2005 <20050131/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE

IN THE BASIC INDEX (/BI) FIELD <<<

=> fil caba

FILE 'CABA' ENTERED AT 15:07:55 ON 31 JAN 2005
COPYRIGHT (C) 2005 CAB INTERNATIONAL (CABI)

FILE COVERS 1973 TO 7 Jan 2005 (20050107/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

The CABA file was reloaded 7 December 2003. Enter HELP RLOAD for details.

=> fil jicst

FILE 'JICST-EPLUS' ENTERED AT 15:08:00 ON 31 JAN 2005
COPYRIGHT (C) 2005 Japan Science and Technology Agency (JST)

FILE COVERS 1985 TO 24 JAN 2005 (20050124/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

=> fil biosis

FILE 'BIOSIS' ENTERED AT 15:08:03 ON 31 JAN 2005
Copyright (c) 2005 The Thomson Corporation.

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 26 January 2005 (20050126/ED)

FILE RELOADED: 19 October 2003.

=> fil mediconf

FILE 'MEDICONF' ENTERED AT 15:08:06 ON 31 JAN 2005
COPYRIGHT (c) 2005 FAIRBASE Datenbank GmbH, Hannover, Germany

FILE LAST UPDATED: 15 NOV 2004 <20041115/UP>
>>> MEDICONF IS NO LONGER BEING UPDATED AS OF 2005 <<<

=> fil conf

FILE 'CONF' ENTERED AT 15:08:09 ON 31 JAN 2005
COPYRIGHT (c) 2005 FIZ Karlsruhe

FILE LAST UPDATED: 28 JAN 2005 <20050128/UP>
FILE COVERS 1976 TO DATE.

=> fil confsci

FILE 'CONFSCI' ENTERED AT 15:08:13 ON 31 JAN 2005
COPYRIGHT (C) 2005 Cambridge Scientific Abstracts (CSA)

FILE COVERS 1973 TO 20 Jan 2005 (20050120/ED)

```
=> fil drugu

FILE 'DRUGU' ENTERED AT 15:08:18 ON 31 JAN 2005
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

FILE LAST UPDATED: 26 JAN 2005       <20050126/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<

>>>  A RECENT REVIEW OF PSYCHIATRIC DISEASE KEYWORDS USED
     IN DERWENT DRUG FILE HAS PROMPTED A REVISION BASED
     ON STANDARD TERMS USED IN DSM-IV (DIAGNOSTIC AND
     STATISTICAL MANUAL OF MENTAL DISORDERS - FOURTH
     EDITION).
     FOR FURTHER DETAILS:
http://thomsonderwent.com/derwenthome/support/userguides/lit_guide


=> fil wpix

FILE 'WPIX' ENTERED AT 15:08:22 ON 31 JAN 2005
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

FILE LAST UPDATED:          28 JAN 2005      <20050128/UP>
MOST RECENT DERWENT UPDATE:     200507        <200507/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
    http://thomsonderwent.com/coverage/latestupdates/           <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://thomsonderwent.com/support/userguides/               <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT
    DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
    FIRST VIEW - FILE WPIFV.
    FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv  <<<

>>> NEW DISPLAY FORMAT HITSTR ADDED ALLOWING DISPLAY OF
    HIT STRUCTURES WITHIN THE BIBLIOGRAPHIC DOCUMENT  <<<

>>> SMILES and ISOSMILES strings are no longer available as
    Derwent Chemistry Resource display fields  <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.
    PLEASE CHECK:
http://thomsonderwent.com/support/dwpiref/reftools/classification/code-revision/
    FOR DETAILS. <<<

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 15:08:26 ON 31 JAN 2005
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
```

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jan 28, 2005 (20050128/UP).

=>
(FILE 'HCAPLUS, MEDLINE, BIOSIS, PASCAL, CABA, JICST-EPLUS, EMBASE, MEDICONF, CONF, CONFSCI, DRUGU, WPIX' ENTERED AT 15:00:58 ON 31 JAN 2005)

=> d que l178
L166 QUE ABB=ON PLU=ON (?NEOPLAS? OR ?CANCER? OR ?CARCIN? O R ?SARCOMA? OR ?LYMPHOM? OR ?MELANOM? OR ?TUMOR? OR ?PROL IFERAT? OR ?LEUKEM? OR ?CHEMOTHERAP? OR ?MYOMA? OR ?HODGK IN?)
L167(29)SEA BORISY, A?/AU
L168(885)SEA KEITH, C?/AU
L169(1714)SEA FOLEY, M?/AU
L170(156)SEA STOCKWELL, B?/AU
L171(16)SEA GAW, D?/AU
L172(2222)SEA NICHOLS, M?/AU
L173(55280)SEA LEE, M?/AU
L174(8556094)SEA L166
L175(8815)SEA (L167 OR L168 OR L169 OR L170 OR L171 OR L172 OR L173) AND L174
L176(53)SEA ?COMBINATORX?/CS,SO,PA
L177(39)SEA L175 AND L176
L178 23 DUP REM L177 (16 DUPLICATES REMOVED)

=> d ibib abs ed l178 1-
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, BIOSIS, WPIX' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 23 ANSWERS - CONTINUE? Y/(N):y

L178 ANSWER 1 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:1059126 HCAPLUS
DOCUMENT NUMBER: 142:32933
TITLE: Combination therapy for the treatment of **neoplasms** using triazoles and antiarrhythmic agents
INVENTOR(S): **Lee, Margaret S.**; Nichols, James M.; Wilson, Amy Beth; Zimmermann, Grant R.
PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

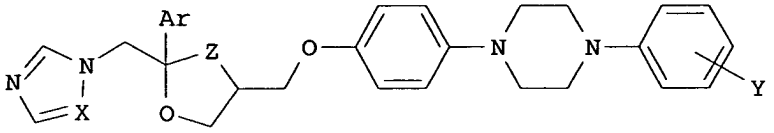
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004105696	A2	20041209	WO 2004-US16314	20040521

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,

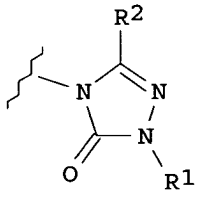
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-473207P P 20030523

GI



I



II

AB The invention features a method for treating a patient who has a **neoplasm** or a patient who is at risk for developing a **neoplasm** by administering to the patient an antiarrhythmic agent in combination with a triazole having the formula I wherein X is CH or N; Z is CH or O; Ar is selected from the group consisting of Ph, thienyl, halothienyl, and substituted Ph having from 1 to 3 substituents, each independently selected from the group consisting of halo, C-C linear or branched alkyl, linear or branched C-C alkoxy, and trifluoromethyl; and Y is a group having the formula II wherein R1 is selected from the group consisting of C1-C6 linear or branched alkyl having 0 or 1-hydroxy substituents and C1-C6 linear or branched alkaryl, and R2 is selected from the group consisting of H, linear or branched C1-C6 alkyl, and C1-C6 alkaryl. The compound of formula I and the antiarrhythmic agent are administered simultaneously or within 28 days of each other in amts. sufficient to inhibit growth of the **neoplasm.**

ED Entered STN: 10 Dec 2004

L178 ANSWER 2 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:718306 HCAPLUS
DOCUMENT NUMBER: 141:218946
TITLE: Combination therapy for the treatment of **neoplasms**
INVENTOR(S): **Lee, Margaret**; Zhang, Yanzhen; **Keith, Curtis**; Wilson, Amy Beth; Auspitz, Benjamin A.; Nichols, James M.
PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004073631	A2	20040902	WO 2004-US4551	20040212

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-447663P P 20030214

AB The invention features methods, kits, and compns. for the treatment of **cancer** and other **proliferative** diseases.

ED Entered STN: 02 Sep 2004

L178 ANSWER 3 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2004:60636 HCAPLUS

DOCUMENT NUMBER: 140:105262

TITLE: Ciclopirox and analogs thereof with optional **antiproliferative** agents for the treatment of **neoplasms**

INVENTOR(S): **Lee, Margaret S.; Keith, Curtis;** Auspitz, Benjamin A.; Zimmermann, Grant R.; **Nichols, M. James**

PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**

SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004007676	A2	20040122	WO 2003-US21783	20030714
WO 2004007676	A3	20040408		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-396120P P 20020715
US 2002-400905P P 20020802

OTHER SOURCE(S): MARPAT 140:105262

AB The invention features a method for treating a patient having a **cancer** or other **neoplasm**, by administering to the patient (i) ciclopirox or a structural or functional analog thereof; and optionally (ii) an **antiproliferative** agent simultaneously or

within 14 days of each other in amts. sufficient to inhibit the growth of the **neoplasm.**
ED Entered STN: 26 Jan 2004

L178 ANSWER 4 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2004:60296 HCAPLUS
DOCUMENT NUMBER: 140:105259
TITLE: Methods using a niclosamide compound and other agents for the treatment of **neoplasms**
INVENTOR(S): **Lee, Margaret S.; Keith, Curtis;** Auspitz, Benjamin A.; Zimmermann, Grant R.; **Nichols, M. James; Foley, Michael A.**
PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004006906	A2	20040122	WO 2003-US22026	20030715
WO 2004006906	A3	20040304		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 2002-396135P P 20020715
US 2002-396136P P 20020715
US 2002-400913P P 20020802
US 2002-400963P P 20020802
US 2003-460203P P 20030403
US 2003-460348P P 20030403

OTHER SOURCE(S): MARPAT 140:105259
AB The invention features a method for treating a patient having a **cancer** or other **neoplasm** by administering a niclosamide, or a structural or functional analog thereof, and, optionally, one or more **antiproliferative** agents in an amount effective to inhibit the growth of the **neoplasm.**
ED Entered STN: 26 Jan 2004

L178 ANSWER 5 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2004:60255 HCAPLUS
DOCUMENT NUMBER: 140:105258
TITLE: Benzimidazole compound-pentamidine compound combinations for the treatment of **neoplasms**
INVENTOR(S): **Borisy, Alexis; Keith, Curtis; Foley, Michael A.; Stockwell, Brent R. ; Gaw, Debra A.**
PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004006849	A2	20040122	WO 2003-US21984	20030715
WO 2004006849	A3	20040603		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-396151P P 20020715
OTHER SOURCE(S): MARPAT 140:105258

AB The invention features a method for treating a patient having a **cancer** or other **neoplasm**, by administering to the patient (i) a benzimidazole or a metabolite or analog thereof; and (ii) pentamidine or a metabolite or analog thereof simultaneously or within 14 days of each other in amts. sufficient to inhibit the growth of the **neoplasm.**

ED Entered STN: 26 Jan 2004

L178 ANSWER 6 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2004:60249 HCAPLUS
DOCUMENT NUMBER: 140:122767
TITLE: Pentamidine compound-chlorpromazine compound combinations for the treatment of **neoplasms**
INVENTOR(S): **Borisy, Alexis; Keith, Curtis; Foley, Michael A.; Stockwell, Brent R. ; Gaw, Debra A.; Nichols, M. James ; Lee, Margaret S.**
PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004006842	A2	20040122	WO 2003-US21803	20030711
WO 2004006842	A3	20040527		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004116407	A1	20040617	US 2003-617424	20030711

PRIORITY APPLN. INFO.: US 2002-395233P P 20020711
OTHER SOURCE(S): MARPAT 140:122767
AB The invention features a method for treating a patient having a **cancer** or other **neoplasm** by administering to the patient pentamidine (or an analog thereof) and chlorpromazine (or an analog thereof) simultaneously or within 14 days of each other in amts. sufficient to treat the patient.
ED Entered STN: 26 Jan 2004

L178 ANSWER 7 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2003:991279 HCAPLUS
DOCUMENT NUMBER: 140:13108
TITLE: Combinations of steroid and azole for the treatment of rheumatoid arthritis
INVENTOR(S): Fong, Jason; Jost-Price, Edward Roydon; **Keith, Curtis**; Manivasakam, Palaniyandi; Sackeyfio, Robyn; Zimmermann, Grant R.
PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003103580	A2	20031218	WO 2003-US17586	20030605
WO 2003103580	A3	20040408		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-387528P P 20020610
AB The invention features a method for treating a patient diagnosed with rheumatoid arthritis by systemically administering an azole and a steroid to the patient. The invention also features a pharmaceutical composition containing an azole and a steroid for the treatment of rheumatoid arthritis. It has been discovered that the combination of an azole and a steroid brings about substantial suppression of TNF-α levels induced in white blood cells.
ED Entered STN: 21 Dec 2003

L178 ANSWER 8 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 2003:892562 HCAPLUS
DOCUMENT NUMBER: 139:375005
TITLE: Drug combinations for the treatment of inflammatory skin disorders
INVENTOR(S): Jost-Price, Edward Roydon; Manivasakam, Palaniyandi; Zimmermann, Grant R.; Fong, Jason; Hurst, Nicole; Auspitz, Benjamin A.; **Nichols, M. James**; **Keith, Curtis**
PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**
SOURCE: PCT Int. Appl., 30 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003092617	A2	20031113	WO 2003-US13760	20030502
WO 2003092617	A3	20040513		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-377475P P 20020503

AB The invention discloses methods for treating a patient who has or is at risk for an inflammatory skin disorder, by topically administering to the patient combinations of drugs (e.g. a prostaglandin and a steroid), either simultaneously or within 14 days of each other, in amts. sufficient to treat the patient.

ED Entered STN: 14 Nov 2003

L178 ANSWER 9 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 2003:551335 HCAPLUS
DOCUMENT NUMBER: 139:111650
TITLE: Prostaglandin-retinoid combination for the treatment of immunoinflammatory disorders and **proliferative** skin diseases
INVENTOR(S): Jost-Price, Edward Roydon; Manivasakam, Palaniyandi; Zimmermann, Grant; Hurst, Nicole; Fong, Jason; **Keith, Curtis; Borisy, Alexis**
PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003057162	A2	20030717	WO 2003-US118	20030102
WO 2003057162	A3	20031224		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-345285P P 20020104

AB The invention provides a method for treating a patient who has an immunoinflammatory disorder or a **proliferative** skin disease, or is at risk for developing an immunoinflammatory disorder or a **proliferative** skin disease, by administering to the patient a prostaglandin and a retinoid simultaneously or within 14 days of each other, in amts. sufficient to reduce or inhibit immunoinflammatory or dermal/epidermal **proliferation.**
ED Entered STN: 18 Jul 2003

L178 ANSWER 10 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 2003:300834 HCAPLUS
DOCUMENT NUMBER: 138:314574
TITLE: Combinations for the treatment of immunoinflammatory disorders
INVENTOR(S): **Keith, Curtis; Borisy, Alexis;** Zimmerman, Grant; Jost-Price, Edward Roydon; Manivasakam, Palaniyandi; Hurst, Nicole; **Foley, Michael A.**
PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003030823	A2	20030417	WO 2002-US31866	20021004
WO 2003030823	A3	20030703		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003119786	A1	20030626	US 2002-264991	20021004
EP 1448205	A2	20040825	EP 2002-800923	20021004
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002013100	A	20041130	BR 2002-13100	20021004
PRIORITY APPLN. INFO.:			US 2001-327674P P	20011005
			WO 2002-US31866 W	20021004

OTHER SOURCE(S): MARPAT 138:314574
AB The invention discloses a method for treating a patient having an immunoinflammatory disorder, by administering to the patient a tetra-substituted pyrimidopyrimidine, and a corticosteroid simultaneously or within 14 days of each other in amts. sufficient to reduce or inhibit immunoinflammation.
ED Entered STN: 18 Apr 2003

L178 ANSWER 11 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 11
ACCESSION NUMBER: 2003:202918 HCAPLUS
DOCUMENT NUMBER: 138:215253
TITLE: A screening system for identifying drug-drug interactions and methods of use thereof

INVENTOR(S): **Borisy, Alexis**; Grau, Daniel; **Stockwell, Brent R.**; **Keith, Curtis**
PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003021264	A1	20030313	WO 2002-US26664	20020822
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
TW 573125	B	20040121	TW 2002-91118282	20020814
EP 1432986	A1	20040630	EP 2002-757293	20020822
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005502049	T2	20050120	JP 2003-525296	20020822

PRIORITY APPLN. INFO.: US 2001-315884P P 20010829
WO 2002-US26664 W 20020822

AB The invention features a method of screening for drug-drug interactions using combinational arrays. The method includes the steps of: (a) providing (i) a test drug; (ii) a drug library; and (iii) an assay, (b) contacting the test drug and at least some of the library drugs from the drug library in the assay under conditions that ensure that each test drug/library drug contacting is segregated from the others, (c) recording the result of the contacting of the test drug and the library drug in the assay, and (d) identifying combinations of drugs that produce a result in the assay that is different from the results produced by either drug of the combination by itself. According to the method, each of the identified combinations indicates an interaction between the test drug and the library drug.

ED Entered STN: 14 Mar 2003
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L178 ANSWER 12 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 12
ACCESSION NUMBER: 2003:521957 HCAPLUS
DOCUMENT NUMBER: 139:190570
TITLE: Systematic discovery of multicomponent therapeutics
AUTHOR(S): **Borisy, Alexis A.**; Elliott, Peter J.; Hurst, Nicole W.; **Lee, Margaret S.**; Lehar, Joseph; Price, E. Roydon; Serbedzija, George; Zimmermann, Grant R.; **Foley, Michael A.**; **Stockwell, Brent R.**; **Keith, Curtis T.**
CORPORATE SOURCE: **CombinatoRx Incorporated, Boston, MA, 02118, USA**
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2003), 100(13), 7977-7982

CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Multicomponent therapies, originating through deliberate mixing of drugs in a clin. setting, through happenstance, and through rational design, have a successful history in a number of areas of medicine, including **cancer**, infectious diseases, and CNS disorders. We have developed a high-throughput screening method for identifying effective combinations of therapeutic compds. We report here that systematic screening of combinations of small mols. reveals unexpected interactions between compds., presumably due to interactions between the pathways on which they act. Through systematic screening of ≈120,000 different two-component combinations of reference-listed drugs, we identified potential multicomponent therapeutics, including (i) fungistatic and analgesic agents that together generate fungicidal activity in drug-resistant Candida albicans, yet do not significantly affect human cells, (ii) glucocorticoid and antiplatelet agents that together suppress the production of **tumor** necrosis factor-α in human primary peripheral blood mononuclear cells, and (iii) antipsychotic and antiprotozoal agents that do not exhibit significant **antitumor** activity alone, yet together prevent the growth of **tumors** in mice. Systematic combination screening may ultimately be useful for exploring the connectivity of biol. pathways and, when performed with reference-listed drugs, may result in the discovery of new combination drug regimens.
ED Entered STN: 09 Jul 2003
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L178 ANSWER 13 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 13
ACCESSION NUMBER: 2002:574927 HCAPLUS
DOCUMENT NUMBER: 137:119655
TITLE: Combinations of drugs (e.g., a benzimidazole and pentamidine) for the treatment of **neoplastic** disorders
INVENTOR(S): **Borisy, Alexis; Keith, Curtis; Foley, Michael A.; Stockwell, Brent R.**
PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002058697	A1	20020801	WO 2002-US1707	20020122
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002165261	A1	20021107	US 2001-768870	20010124
US 6693125	B2	20040217		

EP 1363625 A1 20031126 EP 2002-709117 20020122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
US 2004063769 A1 20040401 US 2003-677664 20031002
PRIORITY APPLN. INFO.: US 2001-768870 A1 20010124
WO 2002-US1707 W 20020122

OTHER SOURCE(S): MARPAT 137:119655

AB The invention features a method for treating a patient having a **cancer** or other **neoplasm**, by administering to the patient (1) a benzimidazole or a metabolite or analog thereof; and (ii) pentamidine or a metabolite or analog thereof simultaneously or within 14 days of each other in amts. sufficient to inhibit the growth of the **neoplasm.**

ED Entered STN: 02 Aug 2002

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L178 ANSWER 14 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 14

ACCESSION NUMBER: 2002:574914 HCAPLUS

DOCUMENT NUMBER: 137:119653

TITLE: Combinations of drugs (e.g., chlorpromazine and pentamidine) for the treatment of **neoplastic** disorders

INVENTOR(S): **Borisy, Alexis; Keith, Curtis; Foley, Michael A.; Stockwell, Brent R.**

PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**

SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002058684	A2	20020801	WO 2001-US47959	20011030
WO 2002058684	A3	20030417		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 6569853	B1	20030527	US 2000-706929	20001106
CA 2436799	AA	20020801	CA 2001-2436799	20011030
EE 200300212	A	20030815	EE 2003-212	20011030
EP 1339399	A2	20030903	EP 2001-994213	20011030
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001015166	A	20031230	BR 2001-15166	20011030
JP 2004517915	T2	20040617	JP 2002-559018	20011030
US 2003166642	A1	20030904	US 2003-347714	20030121
US 6846816	B2	20050125		
NO 2003002036	A	20030704	NO 2003-2036	20030506
BG 107831	A	20040227	BG 2003-107831	20030520
PRIORITY APPLN. INFO.:			US 2000-706929	A1 20001106

WO 2001-US47959 W 20011030

OTHER SOURCE(S): MARPAT 137:119653

AB The invention features a method for treating a patient having a **cancer** or other **neoplasm**, by administering to the patient (i) chlorpromazine or a metabolite or analog thereof; and (ii) pentamidine or a metabolite or analog thereof simultaneously or within 14 days of each other in amts. sufficient to inhibit the growth of the **neoplasm.**

ED Entered STN: 02 Aug 2002

L178 ANSWER 15 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 15

ACCESSION NUMBER: 2002:31138 HCAPLUS

DOCUMENT NUMBER: 136:79719

TITLE: Methods for identifying combinations of entities as therapeutics

INVENTOR(S): **Stockwell, Brent R.; Borisy, Alexis ; Foley, Michael A.**

PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**

SOURCE: Eur. Pat. Appl., 23 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1170591	A2	20020109	EP 2001-115703	20010705
EP 1170591	A3	20020918		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002019010	A1	20020214	US 2001-815417	20010322
US 2002019011	A1	20020214	US 2001-815429	20010322
NZ 524186	A	20041029	NZ 2001-524186	20010701
WO 2002004946	A2	20020117	WO 2001-US21292	20010705
WO 2002004946	A3	20030123		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2352515	AA	20020107	CA 2001-2352515	20010706
NZ 512821	A	20030530	NZ 2001-512821	20010706
BR 2001002781	A	20020312	BR 2001-2781	20010709
JP 2002328124	A2	20021115	JP 2001-208607	20010709
PRIORITY APPLN. INFO.:			US 2000-611835 A	20000707

AB The invention features a method of screening two-entity or higher order combinations for biol. activity using combinational arrays. The method includes the steps of: (a) providing the entities, (b) creating an array of combinations of entities, (c) providing a test element that includes one or more distinct biol. moieties, (d) contacting the array of combinations of entities with the test element under conditions that ensure that each entity/test element contacting is segregated from the others, (e) detecting or measuring a property of the test element, and (f) identifying combinations of entities that cause an effect on the property of the test element that is different from the effect of an entity of the

combination by itself.
ED Entered STN: 11 Jan 2002

L178 ANSWER 16 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:14140 HCAPLUS
DOCUMENT NUMBER: 142:86631
TITLE: Combination therapy with HMG-CoA reductase inhibitor and azole for the treatment of **neoplasms**
INVENTOR(S): **Lee, Margaret S.**; **Nichols, M. James**; Wilson, Amy B.; Zimmermann, Grant R.
PATENT ASSIGNEE(S): **Combinatorx, Inc., USA**
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005000208	A2	20050106	WO 2004-US16653	20040527

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-474704P P 20030530
AB The invention features compns., methods, and kits for the treatment of **neoplasms** using an HMG-CoA reductase inhibitor and an azole. Simvastatin and itraconazole inhibited non-small cell lung **carcinoma** A549 cells.
ED Entered STN: 07 Jan 2005

L178 ANSWER 17 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:308358 HCAPLUS
DOCUMENT NUMBER: 140:315066
TITLE: Methods and reagents using selective serotonin reuptake inhibitors (SSRIs) and corticosteroids for the treatment of diseases and disorders associated with increased levels of proinflammatory cytokines
INVENTOR(S): Manivasakam, Palaniyandi; Smith, Brendan; Fong, Jason; Auspitz, Benjamin A.; **Nichols, M. James**; **Keith, Curtis**; Zimmermann, Grant R.; Brasher, Bradley B.; Sachs, Noah; Chappell, Todd W.; Jost-Price, Edward Roydon
PATENT ASSIGNEE(S): **Combinatorx, Incorporated, USA**
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2004030618	A2	20040415	WO 2003-US30156 20030924

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 2002-413040P P 20020924
US 2002-417261P P 20021009
US 2002-427424P P 20021119
US 2002-427526P P 20021119
US 2003-464753P P 20030423

AB The invention discloses a method for treating a patient diagnosed with, or at risk of developing, an immunoinflammatory disorder by administering an SSRI or analog or metabolite thereof and, optionally, a corticosteroid or other compound, to the patient. The invention also features a pharmaceutical composition containing an SSRI or analog or metabolite thereof and a corticosteroid or other compound for the treatment or prevention of an immunoinflammatory disorder.

ED Entered STN: 15 Apr 2004

L178 ANSWER 18 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:165130 BIOSIS
DOCUMENT NUMBER: PREV200400168939
TITLE: Combinations of drugs (e.g., a benzimidazole and pentamidine) for the treatment of **neoplastic** disorders.
AUTHOR(S): **Borisy, Alexis** [Inventor, Reprint Author]; **Keith, Curtis** [Inventor]; **Foley, Michael A.** [Inventor]; **Stockwell, Brent R.** [Inventor]
CORPORATE SOURCE: ASSIGNEE: **CombinatoRx Incorporated, Boston, MA, USA**
PATENT INFORMATION: US 6693125 February 17, 2004
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Feb 17 2004) Vol. 1279, No. 3. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Mar 2004
Last Updated on STN: 24 Mar 2004

AB The invention features a method for treating a patient having a **cancer** or other **neoplasm**, by administering to the patient (i) a benzimidazole or a metabolite or analog thereof; and (ii) pentamidine or a metabolite or analog thereof simultaneously or within 14 days of each other in amounts sufficient to inhibit the growth of the **neoplasm.**

ED Entered STN: 24 Mar 2004
Last Updated on STN: 24 Mar 2004

L178 ANSWER 19 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:302139 BIOSIS
DOCUMENT NUMBER: PREV200300302139

TITLE: Combinations of chlorpromazine and pentamidine for the treatment of **neoplastic** disorders.
AUTHOR(S): **Borisy, Alexis** [Inventor, Reprint Author]; **Keith, Curtis** [Inventor]; **Foley, Michael A.** [Inventor]; **Stockwell, Brent R.** [Inventor]
CORPORATE SOURCE: Boston, MA, USA
ASSIGNEE: **CombinatoRx, Incorporated, Boston, MA, USA**
PATENT INFORMATION: US 6569853 May 27, 2003
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (May 27 2003) Vol. 1270, No. 4. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Jun 2003
Last Updated on STN: 25 Jun 2003

AB The invention features a method for treating a patient having a **cancer** or other **neoplasm**, by administering to the patient (i) chlorpromazine or a metabolite or analog thereof; and (ii) pentamidine or a metabolite or analog thereof simultaneously or within 14 days of each other in amounts sufficient to inhibit the growth of the **neoplasm.**
ED Entered STN: 25 Jun 2003
Last Updated on STN: 25 Jun 2003

L178 ANSWER 20 OF 23 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-065944 [07] WPIX
CROSS REFERENCE: 2002-149575 [20]; 2003-290239 [28]
DOC. NO. NON-CPI: N2005-057139
TITLE: Evaluating method of combinational composition e.g. of drug, involves producing constituent and assay arrays respectively for constituent compositions and its member, to evaluate effect of composition at each location of assay array.
DERWENT CLASS: S03 T01
INVENTOR(S): **BORISY, A**; **FOLEY, M A**; FONG, J; HURST, N; JOST-PRICE, E R; **KEITH, C T**; **LEE, M S**; LEHAR, J; MOLNAR, R A; SERBEDZIJA, G; **STOCKWELL, B**; ZIMMERMANN, G
PATENT ASSIGNEE(S): (BORI-I) BORISY A; (FOLE-I) FOLEY M A; (FONG-I) FONG J; (HURS-I) HURST N; (JOST-I) JOST-PRICE E R; (KEIT-I) KEITH C T; (LEEM-I) LEE M S; (LEHA-I) LEHAR J; (MOLN-I) MOLNAR R A; (SERB-I) SERBEDZIJA G; (STOC-I) STOCKWELL B; (ZIMM-I) ZIMMERMANN G; (COMB-N) **COMBINATORX INC**
COUNTRY COUNT: 108
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004109280	A2	20041216 (200507)*			103
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
US 2004253627	A1	20041216 (200507)			
US 2004253642	A1	20041216 (200507)			

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2004109280	A2		WO 2004-US18155	20040607
US 2004253627	A1	CIP of	US 2000-611835	20000707
		Provisional	US 2001-315884P	20010829
		CIP of	US 2002-223882	20020820
		Provisional	US 2003-476342P	20030606
			US 2004-863594	20040607
US 2004253642	A1	Provisional	US 2003-476342P	20030606
			US 2004-863592	20040607

PRIORITY APPLN. INFO: US 2003-476342P 20030606; US
2000-611835 20000707; US
2001-315884P 20010829; US
2002-223882 20020820; US
2004-863594 20040607; US
2004-863592 20040607

AN 2005-065944 [07] WPIX
CR 2002-149575 [20]; 2003-290239 [28]
AB WO2004109280 A UPAB: 20050128
NOVELTY - A constituent array of locations associated with a specific concentration of constituent composition e.g. composition of drug, is provided for each composition. An assay array is provided corresponding to a member of set of combined compositions, such that each location of the assay array is associated with the designated aliquot of constituent array. The effect of the composition is evaluated at each location of assay array.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) method of evaluating the activity of compositions in an array;

(2) assay array having a set of combined compositions;

(3) set of arrays for evaluating the activity of combined compositions;

(4) set of constituent array for producing an assay array; and

(5) computer program product for evaluating combinational effect in an assay array.

USE - For evaluating the effect of combined composition of constituents e.g. drug, chemicals, therapeutics in chemical synthesizes and analysis and to evaluate the benefits or toxicity of mixture or chemical on given biological moiety, by determining the changes in composition using an assay array (claimed) e.g. disease-model assay, cytoblot assay, a reporter gene assay, components of fluorescence resonance energy transfer assay, a fluorescent calcium binding indicator dye, etc., and also for measuring the products of deoxyribo nucleic acid (DNA) synthesis, metabolic product of particular cell type, anti-**proliferative** activity, cell viability, variations in cell morphology, proinflammatory cytokine-suppressing activity, etc.

ADVANTAGE - Accelerates evaluation of the activity of combined compositions in reliable and data-rich manner with improved accuracy.

DESCRIPTION OF DRAWING(S) - The figure shows the configurations of constituent array used in evaluating the combinational effect of constituents.

origin sets 410,420,430,440
locations of derivative groups 411,421
constituent arrays 415,425,445
Dwg.4/27

ED 20050128

L178 ANSWER 21 OF 23 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-191038 [18] WPIX
DOC. NO. CPI: C2004-075270
TITLE: Composition useful for treating fungal infection comprises aromatic diamidine compound and hydrazinopyridine compound or quaternary ammonium compound.
DERWENT CLASS: B05 C03 D13 D21 D22
INVENTOR(S): AUSPITZ, B A; **GAW, D A**; JOHANSEN, L M; **KEITH, C**; NICHOLS, J M; SERBEDZIJA, G N; ZIMMERMANN, G R
PATENT ASSIGNEE(S): (COMB-N) **COMBINATORX INC**
COUNTRY COUNT: 104
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004002430	A2	20040108	(200418)*	EN	69
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2003258983	A1	20040119	(200447)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004002430	A2	WO 2003-US20737	20030630
AU 2003258983	A1	AU 2003-258983	20030630

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003258983	A1 Based on	WO 2004002430

PRIORITY APPLN. INFO: US 2002-393155P 20020702; US 2002-393034P 20020628
AN 2004-191038 [18] WPIX
AB WO2004002430 A UPAB: 20040316
NOVELTY - Composition comprises an aromatic diamidine compound (I) or its analogs and a hydrazinopyridine compound (II) or a quaternary ammonium compound (III).

DETAILED DESCRIPTION - Composition comprises an aromatic diamidine of formula (I) or its analogs and a hydrazinopyridine compound of formula (II), or a quaternary ammonium compound of formula N+(R25)3-(CH2)n-N+(R25)3 (III).

A = X-(CH2)p-Y, N(R5)-C(=X)-Y or a group of formula (i) or (ii);
X, Y = O, NR10 or S;
R5, R10 = H or 1-6C alkyl;
R6-R9 = H, 1-6C alkyl, halo, 1-6C alkoxy, 6-18C aryloxy or 6-18C aryl-1-6C alkoxy;
p = 2-6;
m, n = 0-2;

R1, R2 = C(=N-R11)(-N-(R12)(R13));
R11 = H, OH or 1-6C alkoxy;
R12 = T;
T = H, 1-6C alkyl, 1-8C cycloalkyl, 1-6C alkoxy-1-6C alkyl, hydroxy-1-6C alkyl, 1-6C alkylamino-1-6C alkyl, amino-1-6C alkyl or 6-18C aryl;
R13 = T, 1-6C alkoxy, carbo(1-6C alkyloxy), carbo(1-18C aryl-1-6C alkoxy) or carbo(6-18C aryloxy), or
R11 + R12 = C(R14)=C(R15), N=C(R16), N=N, C(R17)(R18)-C(R19)(R20) or a group of formula (iii);
R17-R20 = H or 1-6C alkyl;
R14-R16 = H, 1-6C alkyl, halo or trifluoromethyl;
R21 = halo, trifluoromethyl, OCF3, NO2, 1-6C alkyloxy or T;
R3, R4 = H, Cl, Br, OH, OCH3, OCF3, NO2 or NH2, or
R3 + R4 = a single bond;
R22, R23 = aryl or T1;
T1 = NH2, H, OH, halo, 1-10C alkyl, 1-10C alkoxyalkyl, hydroxy-1-10C alkyl, amino-1-10C alkyl, 1-10C alkylaminoalkyl, 1-10C cycloalkyl or 1-10C alkylaryl, and
R25 = T1 or 6-8C aryl.

INDEPENDENT CLAIMS are included for the following:

(1) a pharmaceutical pack comprising (I) and (II) or (III);

(2) identification of combinations of compounds useful for treating fungal infection which comprises contacting the fungal cells in vitro with (I), (II) and/or (III) and a test compound and determining if the combination of (I), (II) and/or (III) and the test compound reduces growth of the fungal cells relative to fungal cells contacted with (I), (II) and/or (III) in the absence of the test compound, and

(3) treating fungal infection which comprises administering an antifungal agent and (I), (II) or (III).

ACTIVITY - Fungicide.

The fungicidal activity of the combination of pentamidine and phenazopyridine was tested against the susceptible culture of Candida albicans strain 17. The suspension cultures of C. albicans were grown at a starting density of 500 cfu/ml in RPMI media supplemented with 2% glucose. The cultures were treated with pentamidine and phenazopyridine at several dilutions. As a control, the culture was left untreated. The culture was also treated only with pentamidine and phenazopyridine separately. Cultures were incubated for 24 hours at 32 deg. C while shaking and the absorbance was recorded. The cultures were further treated by removal of compounds by plating. It was observed that the MIC70 of pentamidine alone was 0.21 mu M, while pentamidine in combination with phenazopyridine (5 mu M) decreased the MIC by greater than 75%. The inhibition of **proliferation** of the cells with pentamidine and pentamidine + phenazopyridine was found to be 70.1% and 84.7%, respectively.

MECHANISM OF ACTION - None given.

USE - Used for treating or inhibiting development of fungal infection (e.g. Candida albicans, Candida krusei, Candida glabrata, Cryptococcus neoformans and Aspergillus spp.) in a patient at risk for developing the infection e.g. Tinea carporis, Tinea pedis, Tinea barbae, Tinea cruris, Tinea versicolor, onychomycosis, perionychomycosis, pityriasis versicolor, Tinea unguium, oral thrush, vaginal candidosis, respiratory tract candicosis, biliary candidosis, esophageal candidosis, urinary tract candidosis, systemic candidosis, mucocutaneous candidosis, mycetoma, cryptococcosis, aspergillosis, mucormycosis, chromoblastomycosis, paracoccidioidomycosis, North American blastomycosis, histoplasmosis, coccidioidomycosis and sporotrichosis, and for preventing, stabilizing or inhibiting the growth of fungal cells on surfaces such as process equipment, water sanitation systems, cooking utensils, food preparation areas and medical devices (including surgical tools, dental

appliances, orthodontic braces, dentures, stents, endoscopy equipment, surgical implants, prosthetic devices, artificial joints, heart valves, pacemakers, vascular grafts, vascular catheters, cerebrospinal fluid shunts, urinary catheters and continuous ambulatory peritoneal dialysis catheters) (all claimed).

The composition is also useful for the preservation of food, beverages, cosmetics (e.g. lotions, creams, gels, ointments, soaps, shampoos, conditioners, antiperspirants, deodorants, mouthwash, contact lens products, enzyme formulations and food ingredients) and contact lens products.

ADVANTAGE - The composition is effective for inhibiting the growth of several resistant fungi. The composition allows the administration of lower doses of each compound, providing improved efficacy with low activity.

Dwg.0/5

ED 20040316

L178 ANSWER 22 OF 23 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-689547 [65] WPIX
DOC. NO. CPI: C2003-189034
TITLE: Composition useful for treating fungal infections e.g. tinea capitis, tinea corporis and tinea pedis comprises a triazole and an aminopyridine.
DERWENT CLASS: B02 B03 C02 D13 D22
INVENTOR(S): AUSPITZ, B A; **KEITH, C**; **NICHOLS, M J**; SERBEDZIJA, G N; ZIMMERMANN, G R
PATENT ASSIGNEE(S): (COMB-N) **COMBINATORX INC**
COUNTRY COUNT: 102
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003066049	A1	20030814	(200365)*	EN	15
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2003212888	A1	20030902	(200425)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003066049	A1	WO 2003-US3039	20030131
AU 2003212888	A1	AU 2003-212888	20030131

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003212888	A1 Based on	WO 2003066049

PRIORITY APPLN. INFO: US 2002-354645P 20020206
AN 2003-689547 [65] WPIX
AB WO2003066049 A UPAB: 20031009
NOVELTY - Composition comprises a triazole, an aminopyridine and a carrier. The triazole and aminopyridine when administered together inhibit

or reduce fungal growth.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a pharmaceutical pack comprising a triazole and an aminopyridine;

(2) use of an aminopyridine in the manufacture of a medicament for the treatment of fungal infection; and

(3) identifying combinations of compounds involving:

(a) contacting fungal cells in vitro with a triazole and/or an aminopyridine and a candidate compound; and

(b) determining whether the combination of triazole and/or aminopyridine and candidate compound reduces growth of the fungal cells relative to fungal cells contacted with the triazole and/or aminopyridine but not contacted with the candidate compound, or fungal cells contacted with the candidate compound but not with the triazole and/or aminopyridine, where the decrease in fungal growth identifies the combination as useful for treating a patient having a fungal infection.

ACTIVITY - Fungicide; Antiseborrheic; Dermatological; Vulnerary.

MECHANISM OF ACTION - Fungal Growth Inhibitor.

A combination comprising fluconazole and phenazopyridine (PZP) was tested for inhibition of **proliferation** of fluconazole-resistant Candida albicans (strain 17) (test 1) and C. albicans (MYA 573) (test 2) using reduction of Alamar Blue as an indicator of cell number. The antifungal susceptibility testing was performed using a method as described in National Committee for Clinical Laboratory Standards. It was observed that fluconazole (65 micro M) alone resulted in no inhibition of **proliferation.** In contrast, a combination of PZP (20 micro M) and fluconazole resulted in 80% and 92% inhibition of **proliferation** for test 1 and test 2 respectively relative to control cultures grown in the absence of both fluconazole and PZP.

USE - The composition is used for treating a patient having a fungal infection (e.g. tinea capitis, tinea corporis, tinea pedis, onychomycosis, perionychomycosis, pityriasis versicolor, oral thrush, vaginal candidosis, respiratory tract candidosis, biliary candidosis, eosophageal candidosis, urinary tract candidosis, systemic candidosis, mucocutaneous candidosis, cryptococcosis, aspergillosis, mucormycosis, paracoccidioidomycosis, North American blastomycosis, histoplasmosis, coccidioidomycosis and sporotrichosis) caused by Candida albicans, Candida krusei, Candida glabrata and Cryptococcus neoformans. For preventing, stabilizing or inhibiting the growth of fungal cells on a surface e.g. process equipment, water sanitation system, cooking utensil, food preparation area and a medical device (e.g. surgical tool, endoscopy equipment, surgical implant, prosthetic device, artificial joint, heart valve, pacemaker, vascular graft, vascular catheter, cerebrospinal fluid shunt, urinary catheter and continuous ambulatory peritoneal dialysis catheter) (all claimed). Also useful as a disinfectant in the treatment of acne, eye infection, mouth infection, toenail infection, fingernail infections, skin infections and wounds; and for the preservation of food, beverages, cosmetics (e.g. lotions, creams, gels, ointments, soaps, shampoos, conditioners, antiperspirants, deodorants, mouthwash, contact lens products, enzyme formulations and food ingredients).

ADVANTAGE - The triazole and aminopyridine when administered together reduce or inhibit fungal growth. The combination allows the administration of a low dose of each compound and less total active compound, providing similar efficacy with less toxicity and reduced costs; and is potent against fluconazole-resistant strains of Candida species The compound, either alone or in combinations has narrow therapeutic index, narrow absorption window in the gastrointestinal tract and a short biological half-life, so that frequent dosing during a day is required in order to sustain the plasma level at a therapeutic level.

Dwg.0/0

ED 20031009

L178 ANSWER 23 OF 23 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-239219 [23] WPIX
DOC. NO. CPI: C2003-061319
TITLE: Treatment of an inflammatory disorder or risk for developing an inflammatory disorder involves simultaneous or within 14 days of administration of a combination of tricyclic antidepressant and corticosteroid.
DERWENT CLASS: B04 B05 B07 D16
INVENTOR(S): **BORISY, A**; FONG, J; HURST, N; JOST-PRICE, E R; **KEITH, C**; MANIVASAKAM, P; SACKEYFIO, R; ZIMMERMAN, G; ZIMMERMANN, G; SACKEYFLO, R
PATENT ASSIGNEE(S): (COMB-N) **COMBINATORX INC**; (BORI-I) BORISY A; (FONG-I) FONG J; (HURS-I) HURST N; (JOST-I) JOST-PRICE E R; (KEIT-I) KEITH C; (MANI-I) MANIVASAKAM P; (SACK-I) SACKEYFIO R; (ZIMM-I) ZIMMERMANN G; (SACK-I) SACKEYFLO R
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003006026	A1	20030123	(200323)*	EN	13
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
US 2003078246	A1	20030424	(200330)		
EP 1414466	A1	20040506	(200430)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
US 2004110734	A1	20040610	(200438)		
US 2004116395	A1	20040617	(200440)		
KR 2004026680	A	20040331	(200446)		
BR 2002011062	A	20040720	(200451)		
AU 2002310511	A1	20030129	(200452)		
JP 2004534841	W	20041118	(200476)		41
MX 2004000222	A1	20040501	(200482)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2003006026	A1		WO 2002-US20142	20020626
US 2003078246	A1	Provisional	US 2001-304089P	20010709
			US 2002-191149	20020709
EP 1414466	A1		EP 2002-737589	20020626
			WO 2002-US20142	20020626
US 2004110734	A1	Provisional	US 2001-304089P	20010709
		Cont of	US 2002-191149	20020709
			US 2003-716823	20031119
US 2004116395	A1	Provisional	US 2001-304089P	20010709
		Cont of	US 2002-191149	20020709
			US 2003-674744	20030929
KR 2004026680	A		KR 2004-700347	20040109
BR 2002011062	A		BR 2002-11062	20020626
			WO 2002-US20142	20020626

AU 2002310511	A1	AU 2002-310511	20020626
JP 2004534841	W	WO 2002-US20142	20020626
		JP 2003-511832	20020626
MX 2004000222	A1	WO 2002-US20142	20020626
		MX 2004-222	20040109

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1414466	A1 Based on	WO 2003006026
BR 2002011062	A Based on	WO 2003006026
AU 2002310511	A1 Based on	WO 2003006026
JP 2004534841	W Based on	WO 2003006026
MX 2004000222	A1 Based on	WO 2003006026

PRIORITY APPLN. INFO: US 2001-304089P 20010709; US
2002-191149 20020709; US
2003-716823 20031119; US
2003-674744 20030929

AN 2003-239219 [23] WPIX

AB WO2003006026 A UPAB: 20030407

NOVELTY - Treatment of an inflammatory disorder or risk for developing an inflammatory disorder involves simultaneous or within 14 days of each other of administration of a combination of tricyclic antidepressant (A) or structural analogs of amoxapine that are not tricyclic antidepressants including clothiapine, perlapine, fluperlapine or dibenz(b,f)(1,4)oxazepine, 2-chloro-11-(4-methyl-1-piperazinyl)-, monohydrochloride; and corticosteroid (B).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a pharmaceutical composition comprising carrier and drugs amoxapine and prednisolone;

(2) a pharmaceutical pack comprising amoxapine and prednisolone; and

(3) a method for identifying combinations of compounds useful for treating a patient having an inflammatory disorder involves contacting cells in vitro with (A) or (B) and a candidate compound and determining whether the combination of (A) or (B) and the candidate compound reduces cytokine levels in the peripheral blood mononuclear cells relative to cells contacted with (A) or (B) but not contacted with the candidate compound or cells contacted with the candidate compound but not with (A) or (B). The reduction of cytokine levels identifies the combination that is useful for treating patients with inflammatory disorder.

ACTIVITY - Antiinflammatory; Antiarthritic; Antirheumatic; Antipsoriatic; Antiulcer; Antiasthmatic; Cerebroprotective; Immunosuppressive; Dermatological; Antidiabetic; Neuroprotective.

MECHANISM OF ACTION - **Tumor** Necrosis Factor Inhibitor (TNF)- alpha . .

A compound dilution matrix was assayed using a TNF- alpha ELISA method. A suspension of diluted peripheral blood mononuclear cells (PBMCs) (100 micro l) contained within each well of a polystyrene 384-well plate was stimulated for secreting TNF- alpha using a final concentration of phorbol 12-myristate 13-acetate (10 ng/ml) and ionomycin (750 ng/ micro l). Amoxapine (0.2 micro M) and prednisolone (1.11 micro M) were added at the time of stimulation. After 16-18 hours of incubation at 37 deg. C, the plate was centrifuged and the supernatant transferred to a white opaque polystyrene 384 well plate coated with an anti-TNF antibody. After a two-hour incubation period, the plate was washed with phosphate buffered saline (PBS) containing Tween 20 (RTM; polyoxyethylene sorbitan monolaurate) (0.1 %) and incubated for an additional one hour with another anti-TNF antibody that was biotin labeled and horseradish peroxidase (HRP)

coupled to strepavidin. After the plate was washed with Tween 20/PBS (RTM) (0.1 %), the HRP substrate (containing luminol, hydrogen peroxide, and an enhancer such as paraiodophenol) was added to each well and light intensity measured. The combination of amoxapine and prednisolone inhibited TNF- alpha by 51 %.

USE - For treating inflammatory disorders or risk of developing the disorder e.g. immunoinflammatory disorder (including rheumatoid arthritis, psoriasis, ulcerative colitis, Crohn's disease and stroke induced brain cell death), autoimmune disorder (e.g. asthma, multiple sclerosis, type I diabetes, systemic lupus erythematosus, scleroderma, systemic sclerosis or Sjogren's syndrome) (all claimed); ankylosing spondylitis, and fibromyalgia.

ADVANTAGE - The combination has the potential to reduce or inhibit inflammation in the patient. The combination suppresses TNF- alpha levels induced in peripheral blood mononuclear cells (PBMCs). The combination modulates the immune response to a greater degree.

Dwg.0/0

ED 20030407

=>

=>